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CONTENTS: ORIGINAL ARTICLES

NUMBER 1, JULY, 1945

Transient Focal Pulmonary Edema. CARLETON B. PEIRCE, EVERETT F. CRUTCHLOW, ARTHUR T. HENDERSON AND JOSEPH W. MCKAY.....	1
Bed Rest in Tuberculosis. WILLIAM M. PECK AND HENRY STUART WILLIS.	15
Bronchography in Pulmonary Tuberculosis. V. Artificial Pneumothorax. B. A. DORMER, J. FRIEDLANDER AND F. J. WILES.....	21
Acid-fast Bacilli in Nontuberculous Pulmonary Disease. RICHARD A. S. CORY.....	36
Incidence of Tuberculosis in Japanese-Americans. H. E. BASS AND G. D. CARLYLE THOMPSON.....	46
Tuberculosis Survey of Food Handlers on the Island of Oahu. JOSEPH E. FERKANNEY AND RICHARD K. C. LEE.....	51
Enzymes as Factors in Resistance to Tuberculosis. BRUNO GERSTL, ROBERT TENNANT AND OSCAR PELZMAN.....	58
The Specific Cytotoxic Action of Tuberculin. DOROTHY H. HEILMAN, WILLIAM H. FELDMAN AND FRANK C. MANN.....	65
Chemotherapy in Experimental Tuberculosis. WINDSOR C. CUTTING, L. P. GEBHARDT, F. PROESCHER AND E. DURRUM.....	73
Sulfadiazine in Experimental Tuberculosis. C. RICHARD SMITH AND FRANK W. OECHSLI.....	83

NUMBER 2, AUGUST, 1945

Tuberculosis in Household Associates. RUTH R. PUFFER, H. C. STEWART AND R. S. GASS.....	89
Tuberculosis among Montana Indians. J. R. MCGIBONY AND A. W. DAHLSTROM	104
Immobilization of Both Lungs. ALVAN L. BARACH.....	122
Bronchography in Pulmonary Tuberculosis. VI. Thoracoplasty. Part 1. B. A. DORMER, J. FRIEDLANDER AND F. J. WILES.....	145
Anatomical Studies on Human Tuberculosis. XVIII. Additional Observations on Progressive Primary Pulmonary Tuberculosis in Adults. KORNEL TERPLAN.....	155
Books.....	164
American Trudeau Society: Officers, Executive Committee, Council Members and Advisory Board, 1945-1946.....	175
Report of the Committee on Rehabilitation.....	176

NUMBER 3, SEPTEMBER, 1945

Blood Cell Counts. WILLIAM N. BERG.....	179
Pleural Shock and Cerebral Embolism. JOHN B. ANDOSCA AND JOHN A. FOLEY.....	221

Family Histories in Tuberculosis. S. E. SIMPSON.....	231
Epidemiology of Tuberculosis in a Mental Hospital. DAVE B. RUSKIN....	248
Bronchography in Pulmonary Tuberculosis. VI. Thoracoplasty. Part 2. B. A. DORMER, J. FRIEDLANDER AND F. J. WILES.....	258
Obituary—Homer L. Sampson, 1880–1945.....	264
American Trudeau Society: Deaths of Members.....	266

NUMBER 4, OCTOBER, 1945

Streptomycin in Experimental Tuberculosis. WILLIAM H. FELDMAN, H. CORWIN HINSHAW AND FRANK C. MANN.....	269✓
Streptothricin in Experimental Tuberculosis. WILLIAM H. FELDMAN AND H. CORWIN HINSHAW.....	299
Chemotherapy of Sulfones and Sulfonamides in Experimental Tuberculosis. M. I. SMITH AND W. T. McCLOSKEY.....	304✓
Anatomical Studies on Human Tuberculosis. XIX. Protracted Primary Tuberculosis in the Adult, with Some Observations on "Lymphoglandular-Endogenous Reinfection (Ghon)." KORNEL TERPLAN....	312
Eosinophilia in Silicosis. WILLIAM J. HABEEB.....	337
Tuberculosis of the Tongue. L. L. TITCHE.....	342
Founders of the National Tuberculosis Association. ROBERT G. PATERSON.	345
American Trudeau Society: Report of the Committee on Tuberculosis in Industry.....	351
Report of the Committee on X-ray Apparatus and Technique.....	352

NUMBER 5, NOVEMBER, 1945

Indications for Intrapleural Pneumonolysis. H. AUBREY JONES.....	355
Diaphragmatic Paralysis and Pneumoperitoneum. HORACE E. CROW AND FRED C. WHELCHER.....	367
Pneumoperitoneum and Diaphragmatic Paralysis. NORMAN LARUE ANDERSON AND WILLIAM DOUGLAS WINN.....	380
Tuberculosis in Children. J. SCHWARZ.....	392
Degree of Tuberculin Sensitivity. ROBERT W. CLARKE.....	424
Streptomycin in Experimental Tuberculosis. GUY P. YOUMANS AND JOHN C. McCARTER.....	432✓
American Trudeau Society: Report of the Committee on Postgraduate Medical Education.....	440
Report of the Committee on Evaluation of Laboratory Procedures.....	442
Report of the Committee on Medical Program.....	443
Report of the California Trudeau Society.....	444
Report of the Minnesota Trudeau Medical Society.....	445
Report of the Illinois Trudeau Society.....	447

NUMBER 6, DECEMBER, 1945

Silicosis. HOWARD DAYMAN.....	449
Poncet's Disease. FRANK SELIGSON.....	463

Treatment of Pulmonary Tuberculosis with Diasone. KENNETH B. OLSON, JENCE F. THOMPSON AND CLARENCE J. ZINTHEO, JR.....	474
Strict Bed Rest in Pulmonary Tuberculosis. HARRY A. BRAY.....	483
Tuberculosis in a Tropical Naval Hospital. EMIL BOGEN AND G. H. STRICKLAND.....	490
End Results of Artificial Pneumothorax. I. V. ALLEN AND C. W. KELLY..	495
A Suction Cabinet for Use in Cavity Aspiration (Monaldi). WARRINER WOODRUFF.....	502
Anatomical Studies on Human Tuberculosis. XX. Disseminated Calcified Small Nodular Hematogenous Pulmonary Tubercles, Incidentally Discovered. KORNEL TERPLAN.....	505
A Comparison of the Tuberculin Patch Test and the Collodion-Tuberculin Test. PAUL SINGER, JOSEPH J. SOTTILARO AND HERMANN VOLLMER..	521
A Modified Tuberculin Patch Test. THOMAS C. GRUBB.....	526
Clorox Digestion. GEORGE M. CAMERON AND RUTH CASTLES.....	530
Medicine as Practiced during the 1840's. WILLIAM DOSITE POSTELL....	534
American Trudeau Society: Tuberculosis Control in Hospitals. A Study Made by the Committee on Hospital Personnel.....	539

TRANSIENT FOCAL PULMONARY EDEMA^{1, 2, 3}

CARLETON B. PEIRCE,⁴ EVERETT F. CRUTCHLOW,⁵ ARTHUR T. HENDERSON
AND JOSEPH W. MCKAY

Roentgenologic studies and the interpretation of the shadows thrown upon the fluoroscopic screen or recorded upon films have become more and more complex with the succeeding years since Francis H. Williams' contributions in April, 1896. Yet, even to-day, the radiologist, phthisiologist and anatomist have much left to discover in the fields of pathologic physiology and functional anatomy, especially as indicated on the roentgenogram.

Of late years, considerable interest has been aroused in fleeting or transient shadows appearing in the lung fields, often associated with an eosinophilia (Loeffler's syndrome). These patients are not particularly ill, and microscopic studies of necropsy material are seldom available. Some of such patients undoubtedly have been admitted to tuberculosis sanatoria for study, probably some have been stigmatized with a diagnosis of pulmonary tuberculosis. The roentgenographic evidence strongly suggests that these variations from the normal are probably due to peritruncal and interstitial edema, rather than to the cellular infiltrate of an infection. Consideration of transient focal pulmonary edema is suggested as the probable patho-physiologic process, perhaps as one of the manifestations of allergy.

The rapid expansion of chest survey projects by industry and government, in the especial demands of wartime for maintenance, at highest level, of good health among workers in defense industries and the efficiency of the Armed Forces, can be a double-edged sword. All those concerned, particularly the specialist in pulmonary disease and the roentgenologist, must be on guard that they maintain a sane attitude in interpreting evident or suspected variants. We are daily impressed with the great interest of whole families as to their pulmonary status, a direct result of the roentgenologic examination of one or more of their members for the Armed Forces.

A. E. Barclay has recently pointed out the vagaries, almost fads, in interpretation of intrathoracic shadows in the past and has given voice to considerable need for caution in the interpretation of chest roentgenograms until one had adequate knowledge of the healthy chest as well as the clinical features of suspected abnormal individuals. Much of our concept of roentgenologic pathology has been

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³ Presented before the Medical Section at the 40th annual meeting of the National Tuberculosis Association, Chicago, Illinois, May 11, 1944.

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constructed on cadaveric anatomy and the relatively few cases in which surgical or necropsy material is available shortly after radiologic examination.

It was not so long ago that one of us had to know more about pulmonary anatomy, in order to assist his colleagues in the medical and surgical diagnosis and treatment of pulmonary disease. The subsequent investigations in gross and microscopic anatomy for comparative analysis of the roentgenographic shadows have been invaluable for our appreciation of the variation of the normal or "healthy" chest as seen in surveys of university students, industrial personnel or recruits for the Armed Forces. With the advent of tomography and the other techniques of body-section radiography, armed with this preparatory knowledge of intrapulmonary anatomy, the tomogram (laminogram, etc.) becomes a facile and fascinating tool for the further analysis of the intrapulmonary detail of arteries, bronchi and other interstitial tissues.

As a further result of such a study of fundamentals, it is to be hoped that many previous misconceptions in the interpretation of intrathoracic shadows can be eliminated, and fewer persons admitted to sanatoria with a diagnosis of tuberculous perihilar adenopathy simply because the Creator has arranged for them to have pulmonary arteries.

Discussion of transient pulmonary shadows on chiefly hypothetical grounds may seem rash in the light of our preceding comments. However, until surgical or necropsy material is available, cogitation on the clinical and radiologic evidence so far in hand should afford some safeguard for the patient from ill-considered dogmatic opinion.

The structure of the lung with its finely divided, aerated parenchymal and supporting tissues, the pulmonary and bronchial arteries, the closely associated bronchial tree, rich venous and lymphatic network, all held in order by the intralobar, interlobular septa and interstitial connective tissue and surrounded almost completely by the visceral pleura, affords opportunity for rapid physiologic change in response to various physical and biochemical states.

The rapid change which can take place in the child's lung should be common knowledge. But there is an apparently greater discrepancy between the actual physical state within the lung and the clinical signs of percussion and auscultation than we were led to believe as students. This may have been a contributing factor in the relative lack of appreciable literature on the subject prior to Loeffler's contributions in 1932 and 1936. Some cases with abnormal local pulmonary densities, apparently not tuberculous, and with eosinophilia had been recorded by Armand-Delille and Madame de Pierredon (1927), Hay and Evans (1928) and Bass (1931). Bass's case did not show appreciable roentgenographic change over a six-month period. This may belong to a "fixed group," on which comment will be made later.

Sisson and Vogt (1929) observed a diffuse increase in pulmonary density throughout the upper half of both lung fields and interpreted it as an acute pulmonary edema, associated with an anaphylactic shock, in a 14 year old boy, occurring fourteen hours after the injection of tetanus antitoxin. At thirty-six

hours there was marked clearing, and complete disappearance in eighty-six hours.

Loeffler's reports in 1932 reviewed 51 cases largely discovered accidentally in the course of serial fluoroscopies and environmental researches. These were characterized by an appreciable discrepancy between the objective findings and the benign clinical course. As a rule, these patients had few and minor symptoms, some elevation of temperature, occasional irritative cough, sometimes fatigue or slight dyspnea. Radiologically, however, they presented fugitive soft, rather amorphous, single or multiple, minimal to extensive, unilateral or bilateral areas of increased pulmonary density which tended to change within a few (three to ten) days, reappear in other areas and suggest almost a fulminating tuberculous infection, quite disproportionate to the subjective features of the individual case.

Minor physical signs predominated, sometimes compatible with minimal tuberculosis, more often widely divergent from that to be expected from the objective evidence of the roentgenograms. Tuberculin reactions were not predominantly positive and no tubercle bacilli were found in the sputum.

The blood commonly presented an eosinophilia to as high as 66 per cent, with an absolute count of 9,000 to 14,000, as contrasted to a considered norm of 320. Some tendency of the eosinophilic curve to follow the fluctuations of the pulmonary change was noted, although not in the nature of the postinfectious eosinophilia. The degree of eosinophilia and the extent of the pulmonary changes showed no parallelism. Neither *Ascaris* larvae nor other parasitic organisms were found to account for the eosinophilia. In his opinion the relative eosinophilia of tuberculosis rarely exceeded 4 to 7 per cent.

Some seasonal increase in July and August was noted.

The course was essentially benign and, in further contrast to tuberculosis, no progression to necrosis nor residual fibrosis was observed. Sedimentation rate was increased but little in a large majority of the cases.

The intrapulmonary changes in periarteritis nodosa, discussed by Hermann (1933), might perhaps have presented changes somewhat similar to those in the series under consideration if observed during his initial stage of edema with fibrinous exudation about the elastica intima and separation of the muscular walls of the arteries by the exudate, or in the second stage of infiltration of media and adventitia by polymorphonuclear cells. However, the subsequent necrosis of the vessel walls, with secondary thrombosis, infarction and hemorrhage into the adventitia would induce considerable scarring, if recovery should ensue. And it is hardly probable that these changes could wax and wane so completely in an interval of less than a fortnight. With the present concept of periarteritis nodosa as a manifestation of a late stage in a chronic allergic state, however, this must be borne in mind.

Faravelli's case (1937) of the young man with slight malaise for two weeks, lack of appetite, vague shoulder pains, slight fever and diffuse increase in density of the left lung, largely peripheral, with complete roentgenographic clearance in

fifteen hours is of interest, especially as to the rapid change in the atypical pulmonary lesion.

Tuberculosis had been suspected in a patient two years previous to the first observation by Nilsha Hansson (1937), who noted a surprisingly rapid clearing of an apical infiltration but with asthma. For two years subsequently the chest remained clear, but in 1933 a small shadow appeared in the parenchyma of the left lung, becoming bilateral; the sputum was negative for tubercle bacilli, the eosinophilia was 11.5 per cent. Following an antrotomy and polypectomy the next year, the pulmonary densities were extensive although the temperature remained normal, eosinophilia was greater than 30 per cent and the sedimentation rate increased to 129. Fleeting changes of the pulmonary densities from base to apex were observed. Hansson considered the possibility of asthmatic atelectasis or an internal exanthematous type of reaction as the cause of the pulmonary changes.

A characteristic pattern was found by Gravesen (1938) in his patient with rapid changes from massive involvement of one lung to similar density in the contralateral field, shifting to patchy areas and clearing within two months. Some fever, an increased sedimentation rate and an eosinophilia declining from 55 per cent were the notable other data. The Mantoux reaction was apparently debatable.

Wharton-Smith and Alexander (1939) commented on the "privet cough" described by Engel as common in China in May, the pollination period for *Ligustrum*. Transitory changes in the lung and eosinophilia were features of 2 illustrative cases. This phenomenon is thought to be a localized allergic edema. They further reported a child who had similar pulmonary changes with eosinophilia of 30 to 54 per cent, but considerable spiking fever. After a temporary improvement over two months, the youngster (age 7) developed a sudden change for the worse and died with a hemolytic streptococcic septicemia. At autopsy there was no evidence of focal parenchymatous lesions as previously seen on the films.

In discussion of this case, Bowen stressed the frequency with which an "allergic pneumonitis" or "allergic pneumonia" is seen in children.

In a review of 355 asthmatics, Saupe (1940) observed unspecific pulmonary infiltrations in 11.6 per cent, some of which were similar to the planiform shadows he had observed in asbestosis. Others were more extensive and homogeneous, some focal and infiltrative. Paranasal sinus disease was common. There was a simultaneous eosinophilia. Of the series, 13 per cent showed roentgenographic evidence of previous tuberculosis.

The most important feature of this series was the description of one woman, observed for three years, who had shown repeated changes in pulmonary shadows, none of which had left any residual scar in resolution. At autopsy no anatomical substrate of the former changes could be found. Comment was made on the difficulty of differentiation by X-ray, in some of these, between an initial focal tuberculous infection or perihilar infiltrate and the nonspecific lesions.

Freund and Samuelson (1940) reviewed 105 cases from the literature (including Loeffler's 51), in connection with their report of a woman aged 25 who had had bronchitis beginning six years before. Despite repeated attacks of asthma and "catarrh," her chest was said to have been roentgenologically normal previously. Density changes were present in the left mid-lung field. During seventeen days' observation, her fever subsided from 100° F., the cough, chest pain and decreased resonance improved. Eosinophilia fluctuated from 11 to 21 per cent, diminishing to 8.5 per cent. Sedimentation rate decreased from 16 to 5. They comment that the condition is commonly so mild that the patient does not consult his physician. "The diagnosis of this symptom complex is of more than mere academic interest, mild as its course and results are. Its recognition is of the utmost importance from the point of view of differential diagnosis from pulmonary tuberculosis."

Harkavy (1941) brings forward more prominently than others the subject of vascular allergy as a causative factor, pointing out that the observations of Lewis and of Dale suggested an antigen-antibody reaction which is supposed to result in the liberation of a histamine-like substance. This leads to an increased vascular permeability and edema, a direct effect on the intimal endothelium. He had found in biopsies of the affected skin of tobacco-sensitive persons a typical perivascular infiltration of eosinophilia with edema. Eight asthmatics (3 having bacterial allergy with sinusitis) who had interstitial pulmonary changes, eosinophilia, an abnormal electrocardiogram and pleural effusion were reported. The polyserositis and polyneuritis observed again raises the question of a periarteritis nodosa.

Soderling (1939) tried intramuscular and intravenous adrenalin in some asthmatic children with transitory pulmonary densities and eosinophilia, but without appreciable effect on the local lesions.

In that regard Zubiani (1940) has noted that adrenalin seems to have little effect on the pulmonary vessels. He suggested a pharmacodynamic action of histamine as a contributory factor in vasodilatation of capillaries to induce this change in the pulmonary pattern. Choline and acetylcholine might play a part in the asthmatic syndrome with action on the bronchial muscle.

Karen and Singer have expended much effort in an attempt to classify the pulmonary infiltrations as to shape, density and size. The duration of the lesion was shorter than that observed in most cases. Their cases 3 and 5 are quite similar to some observed in our series. Their paper is of importance chiefly in pointing out the similarity of many of these focal areas of increased lung density to the parenchymatous lesions of tuberculosis. The danger of positive diagnosis on one roentgenographic examination is obvious.

Treu (1943) has reported from Calcutta 2 rather characteristic cases of the syndrome which are quite different from the series of so-called "eosinophile lung" reported from southern India by Frimodt-Moeller and Barton. Both of Treu's cases had been considered tuberculous. Both recovered.

Glenn's (1943) case is of interest in that it also was thought to be tuberculous,

but especially that it introduces a different type of possible irritant source as allergen in the nature of an epidermophytosis. No fungi were found in the sputum. Tuberculosis was excluded by a direct examination of sputum and by guinea pig inoculations. The lung fields cleared in two months after considerable variation and shift of the pulmonary densities.

CASE REPORTS

Case 1: A. R. (41-8618), *aet.* 14, had had asthma for four years, was allergic to ragweed. On admission she was in acute respiratory distress. On admission the temperature was 99°F., subsiding the next day to normal and remaining so. Paranasal sinuses were cloudy on X-ray examination; washings produced fairly large amounts of *Hemophilus influenzae*. Musical râles, rhonchi, scattered moist râles and prolonged expiration were observed on clinical examination of the chest.

Roentgenogram (22034 R.V.H.) of chest, December 5, 1943, showed parenchymatous haze and clouds with some lobular pneumonia. Check-up film on December 22, 1943 manifested no residuum—an essentially normal appearance.

White cell count on December 5, 1943 was 14,500, on December 8, 8,200 with 8 per cent eosinophils.

Case 2: N. W. (43-15203), male, *aet.* 33, had had a chronic cough for two years, no allergic history although he was hypersensitive to aspirin, morphine and codeine. He was admitted in acute asthma without elevation of temperature. Allergic response to various antigens was mixed. There was both X-ray and clinical evidence of chronic bilateral maxillary and ethmoid sinusitis with nasal polypi and edema of the mucous membranes. Bacteriologic studies identified only the usual flora. Scattered rhonchi and moist râles were found on clinical examination.

Roentgenograms (59585 R.V.R.) showed only parenchymal haze and slight peritruncal accentuation, no marked changes. White cell count was 8,000, sedimentation rate 15 mm.

This case was incompletely studied, due to various factors. Discharged improved.

Case 3: A. H. (41-3443), male, *aet.* 33, had had asthma and sinusitis for some time, more during the previous year, with urticaria in the periauricular area. On admission in November, 1941 his temperature reached 100°F., subsiding rapidly to normal. Antral washings afforded a moderate growth of *Staphylococcus pyogenes*. Eosinophilia in 1940 varied between 13 and 35 per cent; in November, 1941 it was 55 per cent and in January, 1942, 57 per cent, the white count having dropped from 23,000 in November, 1940 to 15,000 in January, 1942 and 14,600 in August, 1942, with an eosinophilia of 34 per cent. Stools contained no parasites. Bone marrow showed hyperplasia of eosinophilic cells. Chest X-ray study at the Montreal General Hospital in 1940 showed vague shadows in both infraclavicular regions. Repeated roentgenograms from August 9, 1941 to September 8, 1942 demonstrated more or less persistent parenchymal haze in the apices and variable parenchymal clouds to nodular zones of increased density in the bases, with some emphysema. Except for the slight residual changes in the apices the lungs were radiologically clear in September, 1942.

The patient had shown some nodules in the skin of the abdomen. Biopsies in September, 1942 confirmed the diagnosis of *periarteritis nodosa* with unusually marked eosinophilia.

Case 4: H. S. (42-13844), male, *aet.* 34, is being reported elsewhere in full (by A.T.H.). He has been followed for the longest time and in greatest detail. His pulmonary history goes back to 1921 (M.G.H.), when the early films showed some change from whose recorded description it seems probable he had a Loeffler's syndrome at that time. The pulmonary changes have run the gamut from parenchymal haze to nodular areas of infiltration. The eosinophilia has been fluctuant and more or less related to the extent of pulmonary changes shown on the roentgenograms. Bacteriologically, the offending organism seemed to be chiefly *H. influenzae*. Autogenous vaccine has apparently aided markedly in his recovery and present well-being which now has lasted over eighteen months.

This man is an example of the group erroneously considered tuberculous, for he had a sojourn in the sanatorium during 1933, being discharged when the diagnosis was not confirmed.

Eosinophilia has ranged as high as 56 per cent, the white count to 60,000 but the relative eosinophilia has not been consistently proportionate to the leucocytosis.

Case 5: (47-9009), male, *aet.* 54, had had asthma for nine years and was admitted in considerable respiratory distress. He had developed a severe eczematoid dermatitis of the hands in 1941, causing considerable difficulty in continuing his occupation. His temperature never exceeded 99°F. Sensitivity to grass and ragweed pollens was found, paranasal sinuses were not appreciably abnormal, sputum culture showed no unusual flora.

White cells were 14,000 with an eosinophilia of 8 per cent on admission, declining to 6,200 three weeks later. The lung fields on X-ray examination (56559 R.V.R.), showed parenchymatous and peritruncal haze in the upper lobe with peritruncal infiltration in both bases. The lungs were subjected to roentgen therapy for the asthmatic distress with complete relief, but consequently control roentgenograms are not valid as comparisons.

Case 6: N. G. (43-9415), male, *aet.* 53, had been an asthmatic for two years. His father had had hay fever. On admission, his temperature was 99°F., spiking to 101°F. on two occasions; moderate sinusitis was present. The lungs presented radiologically considerable areas of parenchymal haze and infiltration strongly suggesting some edema, shifting from place to place. Sputum culture yielded considerable growth of *Hemophilus influenzae* with the other usual flora.

The white cells dropped from 22,400 on admission to 11,000 a month later, although the eosinophilia remained high, 37 to 40 per cent. The sedimentation rate dropped from 53 to 31 mm.

He was discharged improved after one month in hospital.

Case 7: G. A. (44-1108), female, *aet.* 23, had had asthma for six months, a mixed allergic state, with rhinitis and allergic sinusitis.

On admission in January, 1944 she seemed quite ill, possibly with a lobular pneumonia. However, her temperature did not exceed 99°F.; on repeated cultures of the sputum *H. influenzae* was isolated and on one occasion a pneumococcus type VI in addition to the usual flora. White cells were 9,000 with 5 per cent eosinophilia and 23 mm. sedimentation rate. Four months later the white cells increased to 20,000 rising to 32,000 in the following eight days, then subsiding to 12,000 in the next fortnight. The relative

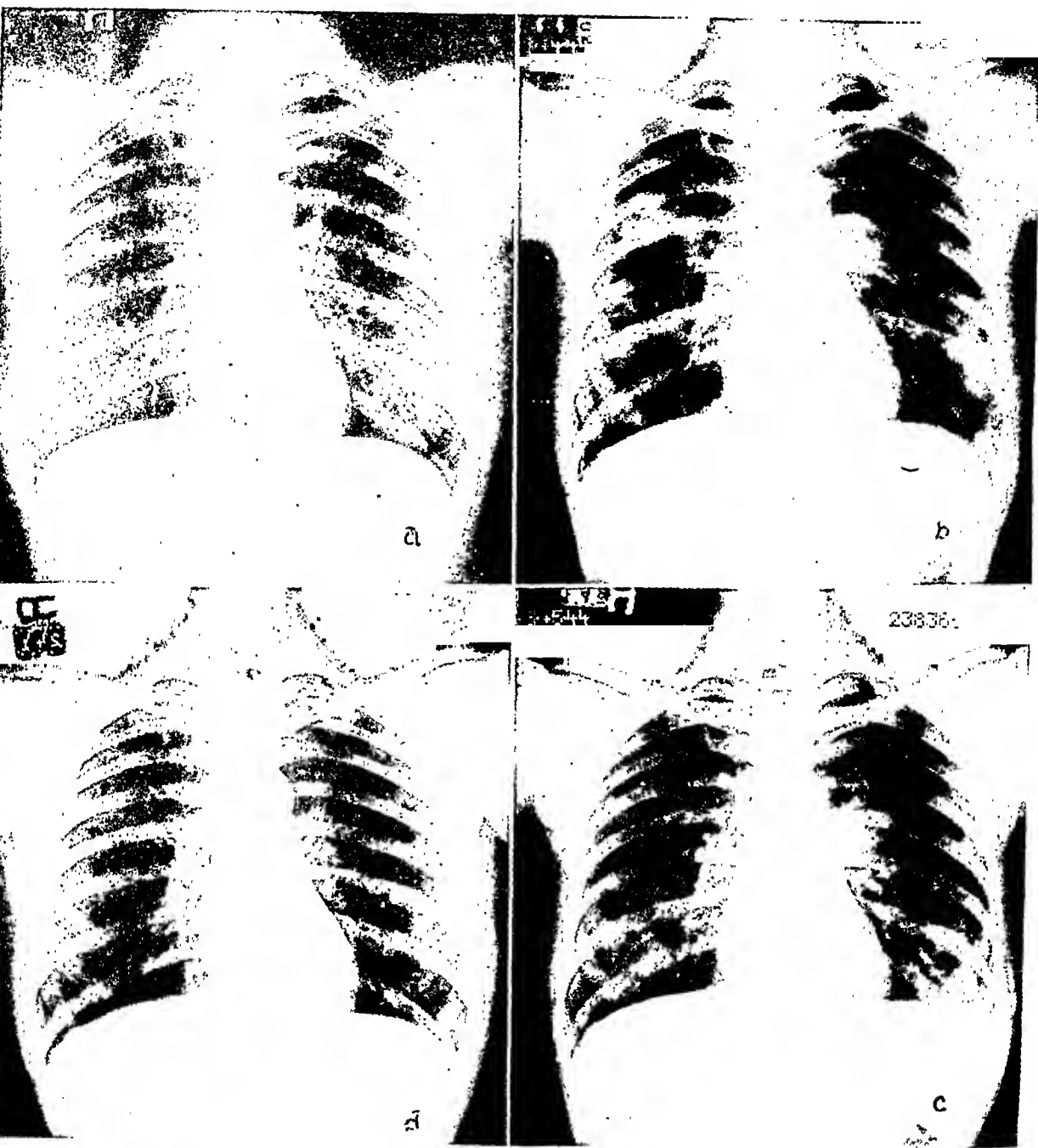


FIG. 1. *Case 7.* (R.V.H. XR 238366/44-1108) Female, aged 23, asthma for six months prior to admission.

(a) January 26, 1944. Seemed quite ill, but temperature not over 99° F. White count 9,000, eosinophils 5 per cent. Chest roentgenologically clear.

(b) April 28, 1944. Clinically improved, but white count 20,000, eosinophils 13 per cent. Roentgenologic evidence of gross, amorphous parenchymal density in both right upper and left lower axillary lung fields.

(c) May 3, 1944. (Five days later) White count 22,000, eosinophils 16 per cent. Previous infiltration gone, but others in the left extreme costophrenic angle and overshadowing left hilum.

(d) May 23, 1944. White count 12,000, eosinophils 20 per cent. Chest roentgenologically clear.

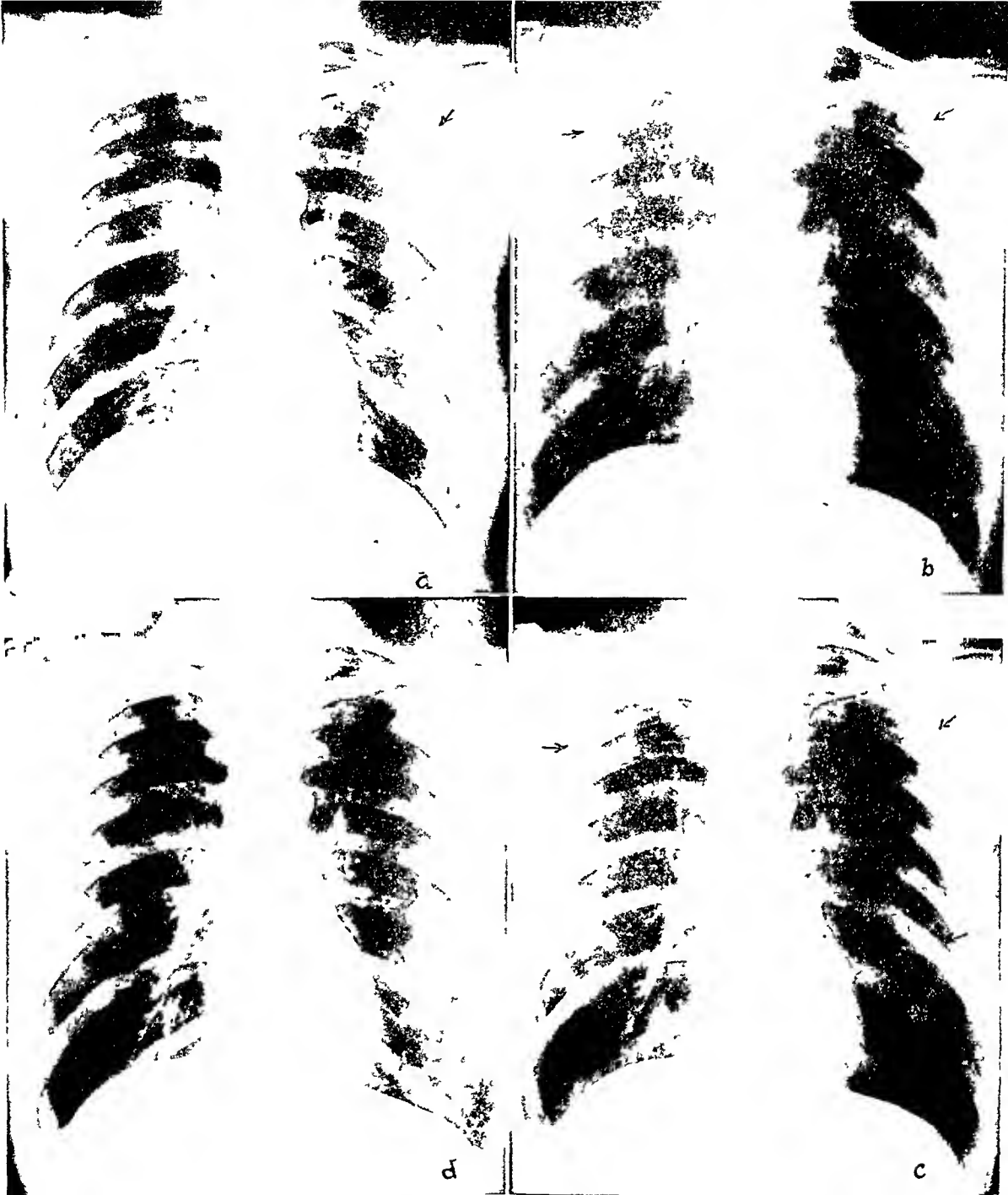


FIG. 2. *Case 8.* (M.G.H. 43-7504) Male, aged 63. Symptomless and apparently well on employment and recheck examinations, until cholecystectomy in August, 1943. Uneventful convalescence.

- (a) October 23, 1943. Anorexia, nausea and night-sweats for three days. Temperature 98° F. No abnormal physical signs in chest. Roentgen examination showed diffuse sub-plural densities in left upper axillary field. October 28, 1943: Eosinophils 58 per cent.
- (b) November 4, 1943. Temperature 103° F., acute pityriasis. Bilateral axillary changes. No physical signs on auscultation.
- (c) November 12, 1943. Readmitted to hospital. White cells 16,000, eosinophils 57 per cent, but no notable physical signs. Roentgenologically improved.
- (d) November 26, 1943. White cells 11,500, eosinophils 19 per cent. Chest essentially clear on X-ray examination.

eosinophilia progressively rose to 13 per cent on May 1, reaching 20 per cent on May 25. The sedimentation rate on May 1 was 53 mm. dropping to 49 mm. by May 25.

The roentgenologic changes were those characteristic of the syndrome with shifting and fleeting zones of parenchymal haze and paratruncal infiltration. She left the hospital improved.

Case 8: H. J. McL., male, *aet.* 63, (M.G.H. 43-7504) was classified in category "A" at the time of a clinical and radiological employment examination on October 7, 1941. A further X-ray check-up on December 9, 1942 showed a normal chest. He recovered readily from a cholecystectomy in August, 1943. On October 23, 1943 he consulted his physician because of anorexia, nausea and night-sweats for the previous three days. His temperature was 98°F. The lungs were clear on physical examination, but radiologically showed diffuse subpleural parenchymal cloudy densities throughout the right upper axillary and the left axillary lung fields with a nodular dense area obliterating the right costophrenic angle. All of this could have been interpreted as evidence of a fulminating pulmonary tuberculosis or diffuse lobular pneumonia, save that its distribution was irregular and not geographically anatomic.

The hemogram of October 28 showed a 58 per cent eosinophilia.

On November 4 he had a temperature of 104°F. and exhibited an extremely itchy erythematous rash over the trunk. His lungs were still clear on auscultation. He was admitted to the hospital (M.G.H.) on November 12, 1943. His blood pressure was 110/60, temperature normal, breath sounds slightly harsh in left lower and right upper chest and there were no râles. Roentgenograms (251393) showed improvement of the lung fields since October 23. White cells were 16,000, with 57 per cent eosinophils. Left axillary nodes were enlarged and tender.

On November 20 his physician noted in the record "Chest examination almost negative. I would never suspect from physical examination the condition found on X-ray examination." Stools contained no ova. Tests for brucellosis were negative.

As of November 26, eosinophilia was 19 per cent. Chest X-ray (251897) appearance had almost cleared on right, improved on left. Clinical diagnosis: *Pityriasis rosea*, Loeffler's syndrome.

A recent report from his physician (May 12, 1944) states that he became well in about four months, and had recently been found "extremely fit."

DISCUSSION

Repeatedly in the literature, notation has been made that the reported case had been considered either a tuberculosis suspect or a positive case. A considerable number of the reported cases and also in our series had clinical symptoms and signs compatible with pulmonary tuberculosis: more or less cough, slight to moderate malaise, loss of weight, changes in physical findings, some crepitant râles, occasionally post-tussive, some history of exposure or indication of previous tuberculosis, some with mildly positive skin reactions. On the other hand, a large number of Loeffler's cases were picked up radiologically on routine surveys.

Loeffler and others have emphasized the relative apparent well-being of the individual patient in contrast to the degree of his roentgenologic and hematologic abnormality. As Freund and Samuelson observed, few have sufficient symptoms, aside from their asthma (to which they may be more or less accustomed), to cause them to consult a physician.

The roentgenologic manifestations of the syndrome may be confused by the uninitiated with an acute focal lesion or the massive involvement of tuberculosis.

However, in our series the X-ray studies presented sufficient characteristics to differentiate the cases from pulmonary tuberculosis. The two main features are the extent and texture of the pulmonary change and the remarkable variability, even in the same patient at any one time or from time to time, as regards size, shape and amount of lung involved. The distribution is not that commonly manifest in tuberculosis. The individual foci are usually associated with the lesser anatomical divisions or segments of the lungs but do not have a true lobular configuration as we know it from anatomical and bronchographic studies. Nor is there an associated peribronchovascular infiltration toward the lung root.

The amorphous character of the individual focus, the appearance of a rapid migration from one portion of lung to another without use of connecting pathways, the transient nature with short duration are notable features. We have not found direct relationship between clinical state and the extent and degree of increased pulmonary density as in the classification made by Karen and Singer.

In general, the texture of the individual roentgenographic shadow is that of a haze or cloud; sometimes so confluent over so great an amount of lung tissue as to suggest consolidation. But yet none have been actually dense enough to be so considered. Any atypical, evanescent parenchymal or peritruncal shadow should be regarded with caution, especially when it does not conform to a common anatomical pattern. Such should be observed frequently over a few days to weeks.

A potential allergic causative factor is strongly suggested in the literature and by our cases. The otherwise unexplainable and marked eosinophilia cannot be disregarded. The fact that rise and fall in degree of eosinophilia does not directly coincide with the extent of the pulmonary involvement is not considered incompatible. The majority of our cases have shown evidence of paranasal sinus disease, predominantly of the edematous type. The majority of our cases had specific allergic sensitivity in some degree. A large number of the cases cited in the literature and the majority of our series had asthma, paranasal sinusitis or periodic bronchitis of undetermined etiology. Several had allergic dermatosis.

What then is the nature of this disturbance which will induce rapidly changing pulmonary densities of an amorphous haze or cloud to ebb and flow, or flit from region to region in the lung? We cannot quite concur with the late Sir Pendrill Varrier-Jones (*Lancet*, 1942, 1, 368) that "we take an X-ray film and are filled with wonder at the complications of nodes and shadows, not sufficiently realizing that what we are gazing at is the picture of past battles, filled-in trenches, exploded mine-craters and the like. What we imagine we see, but do not, is the advancing army of disease . . . We have interpreted the X-ray film wrongly—we have used it as a picture of the present battle, whereas it is but the shadow of past conflicts." For in the most severe case (no. 4) which has been closely followed by one of us (A. T. H.) over a considerable period there is now no appreciable evidence of the "past conflicts" which radiologically were often alarming. Attention has already been called to the lack of residual substrate in the cases which have subsequently come to necropsy (Saupe, Wharton-Smith).

Sisson and Vogt's case is indicative of the possible extreme involvement which can take place in the anaphylactic episode and rapidly resolve without residual trace.

Oertel has pointed out that "Edema occurs without any such tremendous acute congestion as is required to produce it experimentally," "mere mechanical pressure of fluid through congested capillaries (is) not the only essential element in the occurrence of edema." This point is supported by the large number of instances in which edema in the lung appears without any heart weakness, as well as by the not uncommon irregular, selective distribution of edema in different lobes and even in parts of lobes. This fact has led to the conception of nutritional and toxic edemata, as a result of which the permeability of pulmonary vessels is increased.

The evanescent character of the occasional almost massive involvement can hardly be conceived to permit serious consideration of a cellular infiltrate as a prominent component of the shadows thrown upon the roentgenograms

On the other hand it is possible that should such an edema recur frequently and persist long enough the mechanical disturbance so effected in the walls of the lesser vessels and the peritruncal connective tissue might produce a pattern similar to that of periarteritis nodosa with subsequent "fixed" state as shown by Hermann's and Bass's cases and one of ours (case 3).

CONCLUSION

It is our belief at the present time that these evanescent and variable areas of increased pulmonary density are focal zones of transient pulmonary edema, probably associated with the allergic state; they are a local manifestation of the individual's response to an allergen elsewhere, not an inflammatory nodule nor a more general reaction.

It is possible that, if such a state should persist long enough, a pattern suggestive of periarteritis nodosa might be established.

Eosinophilia and roentgenographic pulmonary involvement are out of all proportion to the clinical evidence of disease.

Under adequate treatment marked improvement is to be expected.

Extreme care must be exercised by the phthisiologist, other chest specialists and the radiologist to ensure that no such cases be stigmatized with the diagnosis of tuberculosis or tuberculosis suspect on one roentgenographic observation. Careful clinical history and physical examination are still required for diagnosis.

CONCLUSION

Es nuestra creencia actualmente que las zonas evanescentes y variables de mayor espesor pulmonar representan zonas focales de edema pulmonar transitorio, asociadas probablemente con el estado alérgico, y siendo una manifestación local de la reacción del individuo a la presencia de un alérgeno en otra parte y no un nódulo inflamatorio o una reacción más general.

Es posible que si tal estado persiste por suficiente tiempo, podría establecerse una patología indicativa de periarteritis nudosa.

La eosinofilia y la invasión pulmonar revelada por los rayos X, no guardan la menor proporción con los signos clínicos de la enfermedad.

Con tratamiento adecuado cabe esperar mejoría decidida.

El tisiólogo, otros especialistas torácicos y el radiólogo, deben desplegar sumo cuidado a fin de no imponer a esos enfermos un estigma de tuberculoso o sospechoso, basado en una sola observación radiográfica. Para el diagnóstico todavía se necesitan una historia clínica y un examen físico cuidadosos.

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DISCUSSION

Dr. C. C. Birkelo, Detroit, Michigan: Doctor Peirce has given us much food for thought. I am sure that many patients of the type he has presented have passed through our hands and been called bronchopneumonias. Our chief difficulty is that as soon as we make a diagnosis of a nontuberculous condition, they are referred elsewhere, and we do not get the necessary laboratory work-up which they should have.

There are, in the main, two types of pulmonary shadows or infiltrations in this group although Loeffler mentions four types. There are those shadows which form small or large areas of consolidation and may be mistaken for either tuberculosis or bronchopneumonias, and second, those which are primarily basal and resemble bronchiectasis.

Of the first group, I should like to show slides of 2 cases which came to our hospital with a diagnosis of tuberculosis. Both gave history of recent colds which had passed and, at the time of entrance, they were without important symptoms. Both cleared in a month's time and were discharged as bronchopneumonias. Their blood picture was within normal limits, but no differential count was made.

Of the second type, namely the bronchiectatic type, I should like to show one case:

J. E.: White male, age 51. Was first admitted to another hospital as an asthmatic and so treated, with some improvement. At this hospital, positive sputum was found and he was sent to us. At our hospital all sputa were negative for tubercle bacilli.

He had no asthmatic attacks while with us, but he showed a gradually rising white cell count which reached 30,000 with eosinophils which went as high as 60 per cent.

White cells gradually decreased but the eosinophil count remained high longer, but it also gradually decreased. Heart and E.K.G. were found to be normal. Bronchoscopy was negative. Sternal tap showed no immature cells. Allergic tests revealed reaction to sweet potatoes, spinach and short ragweed, house dust and *B. coli communis*.

Final diagnosis: Basic allergy to account for eosinophilia; bronchiectasis.

The patient was discharged to the Out-Patient Department. His last blood count was in April, 1944: white count normal; eosinophils 5 per cent.

BED-REST IN TUBERCULOSIS¹

Its Dangers and Proprieties

WILLIAM M. PECK AND HENRY STUART WILLIS

Current interest in the dangers from bed-rest challenges those who treat tuberculosis because this disease represents the classical example in which bed-rest is the accepted and approved mode of treatment. If bed-rest exerts a baneful influence on people ill of other disease, should it not hold the same dangers for tuberculous patients? And if the dangers do apply, are they commensurate with the risk which patients must take from tuberculosis treated without bed-rest?

What are these dangers of bed-rest? Some of them have been mentioned prominently in connection with other diseases and are under close scrutiny at present. Some are specific, some are general and others are more or less peculiar to the care of tuberculous patients. Dangers pertinent to rest in tuberculosis are: (1) pulmonary infarction; (2) inadequate drainage of pulmonary lesions; (3) emotional maladjustment; and (4) improper correlation with collapse therapy. Brief discussion of these points seems to be indicated.

DANGERS OF BED-REST

(1) *Pulmonary infarction*: Current thought suggests pulmonary infarction as a danger of paramount importance in people kept abed. What does the record show for the occurrence of this complication in the bed-fast tuberculous person? A certain amount of data is at hand on this question. The Wm. H. Maybury Sanatorium has employed bed-rest and collapse therapy for almost twenty years. It has 845 beds which are usually occupied. Approximately one-half of the patients at any given time will be on a strict bed-rest regimen which does not allow the patient to leave his bed during the twenty-four-hour day. Such bed-fast patients fall into two groups: one comprises terminal patients who remain abed until death supervenes; the other embraces the average new admission and many of the longer-term patients who offer reasonable prospect of recovery. These patients remain on a strict bed-rest regimen for weeks or, more often, for months before bathroom privileges are gradually added to their routine. In this way a period of three or four months of modified bed-rest may occupy the interim between the term of strict bed-rest and exercise.

The first group furnishes nearly all of the postmortem material, analysis of which may be of interest. For eighteen years this institution has operated with a full-time pathologist. In this time 1,682 patients have died in residence, representing 14.6 per cent of all admissions. Of these, 751, or 44.6 per cent, have come to postmortem examination. No selection was shown in obtaining autopsies—the industry and finesse of the physician and the caprice of the relatives being the only determining factors. These 751 autopsies have yielded patho-

¹ From Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

logical signs of pulmonary embolism in 11 cases,² an incidence of 1.5 per cent. Nine of these belonged to the group of terminal patients so that the final prognosis was altered in no way by the occurrence of infarction. Each of the 2 remaining patients had a poor, but not necessarily hopeless, prognosis. Thus in only 2 instances out of 751 autopsies could infarction appear to have contributed to the fatality.

This low incidence of infarction is remarkable when one considers that in most instances dying from tuberculosis is characteristically protracted. Terminal patients often insist religiously upon lying in one position for many hours at a time for fear of inducing cough or hemoptysis by moving. This should favor the development of phlebothrombi; on the other hand, such terminal patients continue to lie quietly in bed until death and, by their inertness, possibly prevent phlebothrombi from giving rise to embolic phenomena. From this experience, pulmonary infarction does not appear to be a danger of great consequence to the tuberculous patient who is kept at bed-rest, particularly when the prognosis of the patient is good.

(2) *Inadequate drainage of pulmonary lesions:* Bed-rest may mean many things to many people. To some its limitations are not breached by any activity of the patient until he places his foot on the floor. This is bed-rest in name only and is therapeutically relatively inert. To others it has an increasing therapeutic value as a state of absolute immobility is approached. Unreasoning adherence to this latter concept fails to take into account the need for pulmonary drainage, especially cavity drainage. In its usual application patients are encouraged to remain in one position, frequently on their backs. Since cavitation is known to occur with notable predilection posteriorly in the chest, the problem of drainage in a recumbent patient should be recognized as vital. Adequate drainage is basic in all other inflammatory processes. Yet by a curious paradox those of us who insist on attention to this principle in all other affections, make no such requirement in tuberculosis, and few of us consider it necessary to determine the precise location of the disease in the lung before putting the patient to bed. The prescription for bed-rest, therefore, should take into account details for positioning the patient at intervals during bed-rest. Otherwise, evacuation of cavities and elimination of pendent secretions must depend on explosive and damaging cough, and the healing process will be retarded. From this point of view may not some so-called "blocked cavities" be only "dependent cavities"? Possibly the phthisiotherapist's neglect of drainage has been encouraged by his tendency to think of the three dimensional chest in terms of a two-dimensional film.

In many sanatoria it is fashionable to apply so-called "postural rest" to pa-

² Included in this list are all patients who showed evidence of either pulmonary infarction or embolism of the pulmonary artery; 5 of these showed the latter only. A good many of the autopsies mentioned in this study were performed in the years before interest in pulmonary embolism became lively. It is possible, therefore, that the examination may have overlooked instances of embolism without infarction; it is unlikely, however, that cases of infarction escaped detection.

tients with unilateral cavitation, especially to those who are awaiting thoracoplasty. The patient is encouraged to lie on his "cavity side" with the idea that the less involved lung will be protected from positive sputum. Is this not specious reasoning? The behavior of iodized oil in the chest during cough suggests that the entire tracheobronchial tree, in the presence of cavity, may be bathed frequently in cavitory contents and thus be contaminated with tubercle bacilli. It would seem, then, that "postural rest" cannot maintain unilateral asepsis. On the other hand, it encourages stagnation of sputum in the cavity and other pendent portions of the lung. These puddled secretions must be eliminated but this can come about only by hard, forceful cough which tends to spread this material indiscriminately throughout the tracheobronchial tree and, by its explosive nature, forces it into the alveoli. Such a scheme is an open invitation to wide-spread extension of disease in either lung.

Examples abound which indicate unintelligent use of bed-rest. For instance, a girl of 13 was admitted from home a few months ago with tuberculous disease involving her right lung. For three months she had been required to remain on a strict bed-rest regimen and to lie always on her affected side. The treatment had been adhered to blindly, and bathing of the dependent side had been withheld during this time so that it had become filthy, though the remainder of her body was scrupulously clean. Secretions from the diseased area appeared to have accumulated even in the larger bronchi leading to the part, and the child presented a lung saturated with its own secretions. Extensive bronchiectasis in the upper lobe was subsequently shown to be present, which may well have developed as a direct result of improper bed-rest.

Several other conditions apt to be present in the tuberculous patient likewise tend to accentuate inadequate drainage. Extrinsic pressure from enlarged lymph nodes in primary tuberculosis and tuberculosis of the bronchus not infrequently produce stasis of secretions resulting in obstructive pneumonitis. The habit of keeping the patient in one position after hemoptysis may likewise contribute to spread of disease through improper drainage of contaminated blood. In chronic tuberculosis a high incidence of associated bronchiectasis exists which must be borne in mind in its need of drainage.

(3) *Emotional maladjustment*: It is a rare person who can accept undaunted a diagnosis of tuberculosis. For him this is a catastrophe of world-shaking magnitude; lifetime ambitions are dashed away and the future suddenly appears inextricably complicated. He could well use the services of a psychiatrist, a sociologist and a philanthropist. Instead, we give him a hospital number, commit him to bed under an inflexible routine and henceforth concern ourselves only with the status of his thoracic contents. Thus we highlight the old saw that, in the mind of the phthisiotherapist, the patient is but "a pair lungs on a pair of legs." We leave the solution of his emotional crises to chance and his adaptation to an unnatural life in bed to nurses whose training is not expected to embrace such matters. Many patients do adapt themselves shortly to their new requirements, but little wonder that evidences of emotional maladjustments show themselves in good number! In this type of patient tenseness, apprehen-

sion or despondency are common, as are a feeling of exhaustion from lying in bed and complaints of muscular pains which lead to constant fidgeting for a comfortable position. Such complaints as anorexia, insomnia, palpitation and constipation are almost routine from him and cough may be unnecessarily severe and damaging. In this way he fails wholly to take bed-rest although he remains in bed. The explanation that such patients tolerate bed-rest poorly in no way relieves us of our responsibility but rather signalizes a lack of bed-side clinical finesse, although it is obvious that a few patients are so constructed mentally as to nullify one's best and most intelligent efforts. Proper bed-rest is too valuable a tool to be used in a haphazard and reckless way. It is wholly worthy of the physician's best attention.

(4) *Improper correlation with collapse therapy*: Bed-rest and collapse therapy are integral and complementary parts of the sanatorium regimen and allow no competition, as divergent schools of thought seem to indicate. It is a fallacy to become so misled by brilliant results that occasionally obtain from bed-rest alone or from collapse alone that one places his entire reliance on a single method. It should be emphasized that a well balanced therapeutic program for the tuberculous patient employs all proved methods of treatment, combining them in the individual case as judgment and experience indicate.

Bed-rest is the foundation therapy, and upon its integrity depends the success of the entire treatment. When of high quality, great confidence may be placed in it, and collapse procedures may be added immediately, deferred for some more favored moment or withheld altogether, depending on the indications—all with the confidence that optimal conditions for recovery have been given to the patient. By thus recognizing bed-rest as a responsible therapeutic instrument, the dangers of overcollapse with curtailment of respiratory function may often be circumvented. In any institution with a well equipped collapse program, exacerbations appear to be related more often to improper rest than to any other factor. In this respect it is a significant commentary that physicians who relegate bed-rest to nursing supervision have little confidence in it and, with just cause, prefer to rely wholly on collapse procedures. Herein lies a real danger, rarely considered.

PROPRIETIES OF BED-REST

What, then, is good bed-rest? What features should be retained and what avoided? Krause has defined rest as relief from strain. In bed-rest, therefore, mental repose and muscular relaxation are the vital features, and any rest regimen which fails to include them cannot fairly be considered a therapeutic procedure. It is a sensitive therapy which, by its results, reflects the care and finesse of its administration. For this reason it must be considered a medical problem to be handled only by physicians of proper temperament and training.

Much time must be spent with a patient in helping him to become adjusted to his changed situation. Psychological, social and economic problems must be discussed with him and simplified. He must be actually indoctrinated with a philosophy which permits him to accept his disease with equanimity and to

submit completely and cheerfully to rigid discipline. Enthusiasm for the future and a will to recover must be stimulated to such a degree that the restrictions of bed-rest seem a small price to pay. Thus the seeds for future rehabilitation are planted at the very inception of treatment and many troublesome emotional maladjustments avoided.

Muscular relaxation comes unnaturally to many patients and may be taught only by daily, painstaking repetition. Once achieved, rest in bed becomes pleasant and comfortable. Although continuous recumbency is desirable, inertness is not wanted, and the patient should be encouraged to seek his own most restful position. On the contrary great insistence should be placed on change of position frequently enough to insure adequate drainage of all parts of the chest. This will involve lying in prone, supine and both lateral positions. Once the exact location of the pulmonary disease has been determined and the relative importance of each position appreciated, more detailed instructions may be given, bearing in mind that stasis of contaminated secretions in normal areas of the lung must be avoided just as zealously as drainage of diseased areas is encouraged. This regimen leads to obvious loss of muscle tone. Such loss, however, does not appear to affect the patient adversely, and the tone is promptly restored when the patient begins to take exercise.

Good bed-rest, accordingly, is a precise method of treatment with clear-cut specifications and is based on three fundamental principles: mental repose, muscular relaxation and adequate drainage. Other details are less important and may vary with the type of nursing care available—this without materially affecting final results. Thus, such questions as assistance with meals, bedpans and baths are of secondary interest. The excuse that facilities for good bed-rest are lacking can be rarely substantiated on any ground save that of insouciance.

The present paper represents our current clinical impressions. Its limitations do not allow discussion of several important points respecting the value of bed-rest. Work is now under way in this institution which is aimed at obtaining more factual data in statistical form on a number of questions, such as how good is a strict bed-rest regimen as compared with a modified one? What is the relation of the healing process to lowered metabolism and other physiological alterations associated with bed-rest? How long should bed-rest be continued in given types of disease?

SUMMARY

1. Pulmonary infarction and embolism of the pulmonary artery were found in 1.5 per cent of 751 autopsies on tuberculous persons.

2. Certain other dangers may be associated with bed-rest in this disease. Among these are the failure:

- a. To obtain adequate pulmonary drainage.
- b. To meet the emotional maladjustment so often present in patients.
- c. To correlate properly collapse therapy and a bed-rest regimen.

3. The evils which adhere to bed-rest are incident to its mode of application.

Good bed-rest will avoid these dangers and retain its full therapeutic value. Poor bed-rest is often therapeutically inert and can be aptly called bed-fatigue.

4. Proper bed-rest should include mental repose, muscular relaxation and adequate pulmonary drainage and should not be thought of as mere regimentation in recumbency.

5. Bed-rest is inherently valuable but unreliable when administered indifferently. It warrants constant, critical attention by the physician in order to insure good results.

SUMARIO

1. En 1.5% de 751 autopsias en tuberculosos, observáronse infarto pulmonar y embolia de la arteria pulmonar.

2. En esta enfermedad el reposo en cama puede acompañarse de ciertos otros peligros, entre los cuales figuran la falta de:

- a. Obtención de una canalización pulmonar adecuada;
- b. Compensación del desajuste afectivo que es tan frecuente en los enfermos, y
- c. Correlación apropiada de la colapsoterapia y del encamamiento.

3. Los males que acompañan al reposo en cama se relacionan con la forma en que se aplica. El reposo apropiado evitará dichos peligros y retendrá su pleno valor terapéutico. El reposo mal aplicado resulta terapéuticamente inactivo y puede más bien llamarse fatiga en cama.

4. El descanso en cama apropiado debe comprender reposo mental, dilatación muscular y canalización pulmonar adecuada sin que deba considerarse como mera regimentación en decúbito.

5. El reposo en cama es en principio valioso pero inseguro si se administra apáticamente, de modo que justifica la constante atención cuidadosa de parte del médico a fin de asegurar el éxito.

BRONCHOGRAPHY IN PULMONARY TUBERCULOSIS¹

V. Artificial Pneumothorax

B. A. DORMER, J. FRIEDLANDER AND F. J. WILES

Previous papers have dealt with early pulmonary tuberculosis, the radiological "black-out," the problem of chronic fibroid phthisis and the geography of the bronchial tree in pulmonary tuberculosis. This one introduces the subject of artificial pneumothorax. This form of treatment remains largely empirical. It works, but nobody has been able to explain precisely why. It is certainly not because of resting the lung or "splinting" the lung. There is retraction of the diseased tissue in the lung. There is lymph stasis, so it is said, and there is increased blood supply. None of these factors, however, adequately explain why pneumothorax is of therapeutic value.

If we study a normal bronchogram in inspiration and expiration, we notice that there is an alveolar filling which is characteristic. There is movement of the whole bronchial tree with respiration and obvious dilatation of the individual bronchi on inspiration. In the bronchogram of an early case of exudative pulmonary tuberculosis, the alveolar pattern is missing in the areas of infiltration and the bronchioles in those areas are blocked.

In a bronchogram of a patient with early exudative disease and a recent, uncomplicated artificial pneumothorax, the alveoli are still not filled in the area of disease. In the area surrounding the actual infiltration the alveolar pattern is not completely absent, but there is definite blockage of some of the bronchioles as compared with a completely healthy lobe of the same lung which shows an alveolar pattern. Even in the healthy lobe the alveolar filling is not as marked as in a normal uncollapsed lung showing that a certain number of alveoli are closed by retraction.

As the refills are continued, fewer bronchioles are seen to be blocked and eventually they all become patent. The alveoli are then seen to be filling again in the diseased lobe, except in the actual area of infiltration where they remain permanently collapsed.

How to explain this phenomenon? In early exudative disease there is blockage of the bronchioles causing areas of atelectasis. The result of this is an area of pneumonitis, tuberculous in nature, and ultimate softening and discharge of contents leading to bronchiectasis and/or cavitation. The cause of the atelectasis is central.

In an artificial pneumothorax the collapse is from the periphery. Reducing the subatmospheric intrapleural pressure allows retraction of the diseased area, and large numbers of alveoli cave in. The general retraction and shrinking of alveoli and connective tissue prevent further infection and tend to squeeze liquefied tuberculous material out of the blocked bronchioles leaving them patent. This allows healing by fibrosis of the approximated thin walls of recent cavities and recent bronchiectasis in the actual area of disease. At the same time

¹ From the King George V Hospital for Tuberculosis, Durban, South Africa.

the surrounding alveoli, which would also have become diseased if their bronchioles had remained blocked, are now able to expand and occupy the space left by the contraction of the fibrosed area. In other words, pneumothorax is effective because it eliminates the blockages in the bronchial system.

It has been shown experimentally that bronchiectasis results from the combined action of bronchial block and infection, and in experimental animals it has been found that artificial pneumothorax does not prevent bronchiectasis when these two factors are in operation (Tannenberg and Pinner (1)). We have noted, however, that if bronchiolar or bronchial block is caused by substances natural to the lung, that is, viscid sputum, containing either tubercle bacilli or other organisms, then artificial pneumothorax will prevent bronchiectasis, if done soon enough, because it relieves the block by squeezing out the viscid plug of sputum. If the block is caused by a foreign body (whether naturally or artificially introduced), then artificial pneumothorax does not prevent bronchiectasis because it cannot get rid of the block. This explains the discrepancy between the unsuccessful use of artificial pneumothorax in experimental animals with a mechanical block and the success of the same treatment in human beings with bronchial block due to viscid sputum, for example in postoperative atelectasis by artificial pneumothorax with complete success in each case. The sputum blocking the bronchi was coughed up shortly after inducing the pneumothorax and within forty-eight hours the lung had reexpanded leaving no residual bronchiectasis.

The converse of our hypothesis is that pneumothorax is of no therapeutic value in a case where the bronchial block persists in spite of the pneumothorax. In such a case we get the picture of ordinary lobar atelectasis within the artificial pneumothorax — the so-called "black lobe." This usually occurs as a result of kinking due to the pull of adhesions or similar causes leading to dislocation of a lobe or bronchus from its normal position. Artificial pneumothorax cannot get rid of such a block; it accentuates it, and unless the normal relationships are quickly established by cutting of adhesions or abandoning the pneumothorax by aspirating the air the end-result is lobar bronchiectasis or lobar cavitation. This lobar collapse or black lobe is one of the worst things that can happen in a case of artificial pneumothorax.

If a bronchogram prior to an attempted artificial pneumothorax shows old-standing thick walled bronchiectatic bronchi or thick walled cavities, then it is of no avail to carry on with this form of treatment, as the ultimate result will be that the bronchiectasis or the cavities will still be present. We have learned from bitter experience that artificial pneumothorax is not a treatment for chronic bronchiectasis of nontuberculous origin or for chronic lung abscess, and logically should not be effective if the origin of these conditions is tuberculous.

Artificial pneumothorax with superatmospheric intrapleural pressure is a relic of the days when it was thought that we ought to collapse a lung in the literal sense of the word. If persisted in, upsetting complications arise, the two most bothersome being tuberculous empyema and bronchopleural fistula.

The movement of the treated lung in unilateral artificial pneumothorax is as

great or greater than in the uncollapsed lung. The swing of the mobile mediastinum is an added factor in what we call the "physiological minuet." In bilateral pneumothorax the movement of the lungs is not so great because of the stability of the mediastinum, but it is still appreciable. In view of this active movement in all directions it is unwise to talk of splinting the lung or putting the lung at rest by means of artificial pneumothorax.

Here then we have presented our theory. Now let us look at our practice. The following cases illustrate in detail the points mentioned in this introduction. They are divided into six groups:

Group 1: Normal bronchogram.

Group 2: The average artificial pneumothorax.

Group 3: Adhesions.

Group 4: Black lobes.

Group 5: Cavities.

Group 6: Tension pneumothorax (superatmospheric pressure).

CASE REPORTS

Group 1. Normal Bronchogram

The first two pictures can be taken as those of a normal bronchogram in inspiration and expiration. Two things are to be noted, namely, the alveolar filling and the bronchial movement. Even the apical bronchi show a well defined downward movement in inspiration. The alveolar filling is much less distinct in inspiration. The increase of bronchial diameter visible to the naked eye is also worthy of comment. (Figures 1 and 2.)

Group 2. The Average Artificial Pneumothorax

Case 2: C. 407, Indian male, aged seventeen years. History dates back for one year when he began to complain of giddiness, tiredness, coughing and of bringing up sputum. He is an ill-looking, thin Indian boy. Temperature and pulse are normal. Sputum contains tubercle bacilli. The physical signs are prolonged expiration and crepitations at both apices.

X-ray film (figure 3) shows infiltration of the right infraclavicular region and a probable cavity in this area of about $1\frac{1}{2} \times 1$ inch. There is scattered infiltration in the left infraclavicular region and midzone extending from the root to the periphery of the lung.

A bronchogram of the right lung (figure 4) shows:

- (1) Blocked bronchioles in the area of infiltration—no alveolar filling.
- (2) The cavity shown in figure 3 is not a true representation of the actual cavity present.
- (3) Normal bronchogram with typical alveolar filling in the lower lobe.

Because of the cavity it was decided to induce an artificial pneumothorax on the right side first.

Figure 5 is a bronchogram done after the induction of the artificial pneumothorax (patient lying down). This shows:

- (1) The size and shape of the cavity which communicates with a bronchus and the lack of alveolar filling in the diseased area.
- (2) The normal bronchogram in the lower lobe, but the shutting off of some alveoli.

The next two figures (6 and 7) are bronchograms (patient standing) showing the movement of the lung on respiration:

- (1) Note the extraordinary movement of the mediastinum, the trachea and bronchi and the lung to the left on expiration.
- (2) Note the vastly increased diameter of the bronchi in inspiration and their general movement.

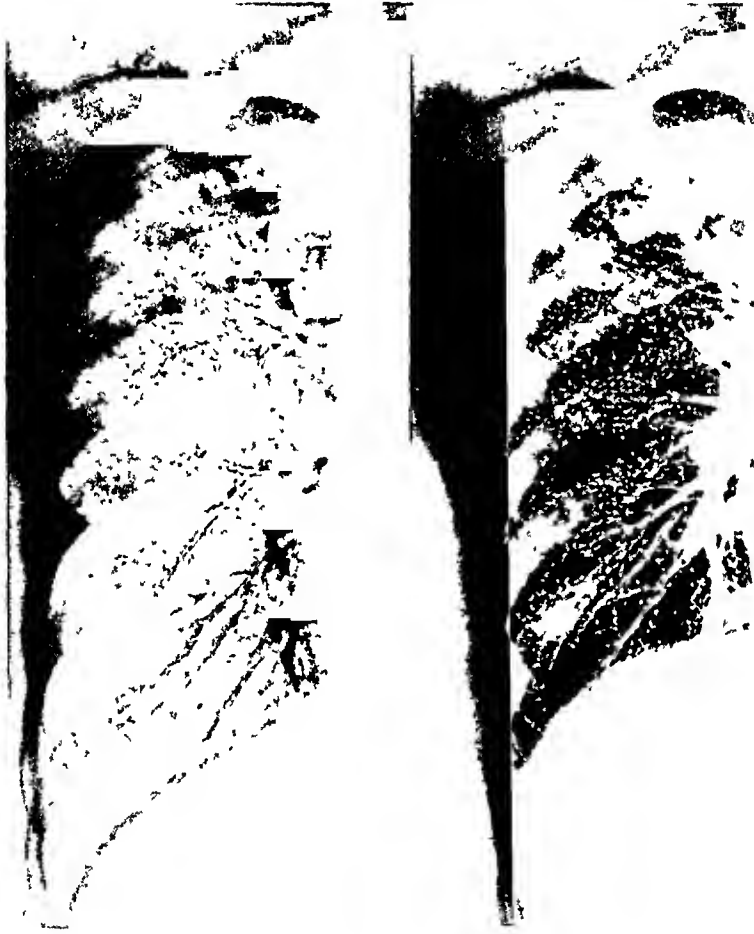


FIG. 1. Left; FIG. 2. Right

- (3) The diseased area is more homogeneous than the normal lung and, although the bronchioles are mostly patent, the alveolar filling is not normal.
- (4) The movement of the diseased area is well shown by the increase in vertical diameter and the decrease in horizontal diameter of the cavity in expiration.
- (5) The bunching together of bronchi in expiration and the wide open motion in inspiration.

Figure 8 is a bilateral bronchogram and shows on the left side blocking of the bronchi in the diseased area in the upper lobe and normal alveolar filling in the lower lobe.

Figures 9 and 10 are bronchograms taken fifteen months later when a bilateral pneumothorax had been established for some months. They are taken in inspiration and expiration. Note:



FIG. 3. Upper left; FIG. 4. Upper centre; FIG. 5 Upper right; FIG. 6. Lower left; FIG. 7. Lower right.



FIG. 8. Top; FIG. 9. Lower left; FIG. 10. Lower right

- (1) The cavity has closed and an area of fibrosis remains. There is now normal alveolar filling throughout the lung, with the exception of the area of fibrosis.
- (2) The absence of mediastinal swing now that the internal structures have been stabilized by the bilateral pneumothorax.
- (3) The wide movement of bronchi with respiration and the considerable increase in their lumen on inspiration.

We consider this series of films important, as it shows our conception of the events occurring in an uncomplicated artificial pneumothorax and of the development of healing.

Case 3: E. 358, European male, aged twenty-two years. He was perfectly fit until four months ago when he had a sudden hemoptysis. After that he began to cough and bring up sputum. He is fit looking. Temperature and pulse are normal. Sputum contains tubercle bacilli. There are no physical signs indicative of disease of the lungs.

An X-ray film showed extensive infiltration of the left infraclavicular and midzones of an exudative type. The right root area was enlarged and fluffy and there was some infiltration of the right lower lobe. The right diaphragm was high and the right interlobar septum appeared to be depressed.

An artificial pneumothorax was induced on the left side.

Figure 11 is a double bronchogram showing:

- (1) The nonfilling of the diseased area on the left, and the well marked alveolar pattern of the rest of the lung.
- (2) The presence of a cavity with pressure on the right main bronchus.
- (3) The normal alveolar picture of the right upper lobe; the lack of alveolar filling of the right base is the result of the partial collapse.

This case is instructive apart from showing the effects of an artificial pneumothorax because the conventional radiograph gave no clue to the cavity in the right root area.

Group 3. Adhesions

Case 4: C. 170, Indian male, aged twenty-one years. He became ill "some time ago" with fever, headache and cough. He thinks it is six weeks since the trouble commenced. He is healthy looking. Temperature is 96 to 99°F.; pulse 80 to 102. Sputum contains tubercle bacilli. The only physical signs are a few crepitations at the right apex.

A roentgenogram showed scattered infiltrations in the right infraclavicular region and midzone. A right artificial pneumothorax was induced. A roentgenogram showed a fairly good pneumothorax with the upper lobe held to the apex by a long thick adhesion.

Figure 12 is a bronchogram showing neither bronchiolar nor alveolar filling of the diseased lobe and normal filling of all sections of the lung in the lower lobe.

Case 5: E. 277, European male, aged twenty-one years. He had no symptoms. He was X-rayed as a routine before employment in a sugar mill and told he had tuberculosis. He is healthy looking. Temperature and pulse are normal. Sputum contains tubercle bacilli. Physical signs are dulness over the right side and a few crepitations at the apex behind.

A roentgenogram (figure 13) shows extensive mottling in the apices, infraclavicular regions and midzones of both lungs.

A consecutive bilateral artificial pneumothorax was induced and a roentgenogram



FIG 11. Upper; FIG. 12 Lower



FIG. 13. Top; FIG. 14. Lower left; FIG. 15. Lower right

showed this bilateral pneumothorax after sections of adhesions on both sides. The left lung was fairly free, but the right lung still showed an adherent apex.

Figures 14 and 15 are bronchograms showing the right and left side, respectively. There is well marked bronchiectasis of both upper lobes, a blocking of the bronchioles in the midzones with failure of alveolar filling and a normal alveolar filling of the lower lobes.

The lesson to learn is that pneumothorax in this type of case is never permanently successful. A pneumothorax is not good treatment for an ordinary bronchiectasis, nor is it successful in a tuberculous bronchiectasis of long standing.

This case had a positive sputum after all the labor of prolonged pneumothorax and adhesion cutting and is responding to intrabronchial treatment with sulphonamide suspension in lipiodol.

Group 4. Black Lobes

Case 6: C. 384, Indian male, aged nineteen years. He gave a history of "chest ache" and cough for six weeks. His brother died of pulmonary tuberculosis. He has no cough nor sputum. He is a thin, healthy looking Indian. Temperature and pulse are normal. Laryngeal mirror test shows tubercle bacilli. There are no physical signs indicative of pulmonary disease.

An X-ray film showed mottling in the right apex and infraclavicular region.

A bronchogram showed bronchiolar block in the region of the infiltration. The rest of the lung showed normal alveolar filling.

The patient was put on strict bed-rest, but some weeks later signs of cavitation appeared in the right upper lobe and a right artificial pneumothorax was induced.

Figures 16 and 17 are bronchograms of the right lung taken in inspiration and expiration. Note:

- (1) The black upper lobe with its cavity.
- (2) The normal filling of the base.
- (3) The marked movement of the internal structures on inspiration and expiration and the bronchial dilatation on inspiration.
- (4) The absence of any bronchial structure in the black lobe.

This case is an example of atelectasis of a lobe as the result of the main bronchus feeding the upper lobe being blocked.

There is a little residual lipiodol on top of the cavity from the first bronchogram taken before the artificial pneumothorax. We should also note the lack of movement of the black lobe as compared with that of the diseased area in the previous artificial pneumothorax cases.

Figure 18 is a lateral bronchogram showing the opaque black lobe setting on top of the normal lower lobe.

A black lobe means the block of a main bronchus, usually due to kinking, and such a lobe should be the signal for the immediate abandonment of the artificial pneumothorax, as failure to do this will eventually lead either to bronchiectasis or to rupture of the cavity. (Just as this paper was completed, this patient developed a spontaneous pneumothorax due to bursting of the cavity in his right upper lobe.)



FIG. 16. Upper left; FIG. 17. Upper right; FIG. 18. Lower

Case 7: E. 124, European female, aged thirty-two years. Three months prior to admission she felt off color and went for a holiday. While away she had a pain in her left side and saw a doctor who examined her sputum and found tubercle bacilli. She is frail looking. Temperature and pulse are normal. Sputum contains tubercle bacilli. There are no physical signs of disease of the lungs.

X-ray examination showed infiltration of the left midzone and lower lobe. An artificial pneumothorax was induced on this side.

As soon as this was fully established it was noticed that the left lower lobe was a black lobe and the pneumothorax was abandoned. However, the resultant bronchiectasis was not obviated as shown by a bronchogram which revealed an extensive retrocardiac bronchiectasis on the left.

Case 8: E. 528, European female, aged nineteen years. For the last year she had been complaining of cough and sputum, loss of weight, loss of appetite and malaise, but was not very concerned about it. A month before admission she had a sudden severe pain in the left side of her chest and saw a doctor who diagnosed pulmonary tuberculosis. She is a thin, ill looking European girl. Temperature is 99 to 100.2°F.; pulse 86 to 120. Sputum contains tubercle bacilli. The physical signs are dulness over both upper lobes with numerous crepitations over this area.

An X-ray film revealed extensive infiltration of the whole of the left lung with several cavities in the upper lobe. There was extensive scattered infiltration throughout the right lung.

An artificial pneumothorax was commenced on the left. This resulted in an adherent apex and a black lobe (figure 19). The pneumothorax was abandoned but a bronchogram, after the lung had reexpanded, showed excavation of the whole left lung, with the exception of a small portion of the left lower lobe (figure 20).

This type of case with old-standing cavitation and fibrosis never clears up on an artificial pneumothorax, even if a perfect technical result free from adhesions is obtained. It is better to leave it alone than to attempt officious pneumothorax therapy.

Group 5. Cavities

Case 9: E. 268, European female, aged twenty years. She had had a dry cough for several years. A month before admission she had a pain in the right side of her chest and difficulty in breathing. She is a healthy, rather "spiritual" type. Her temperature and pulse are normal. Sputum contains tubercle bacilli. The physical signs are crepitations over the right apex and dulness with crepitations over the right base.

An X-ray film (figure 21) shows extensive disease throughout the right lung, mostly productive in character with cavities in the right infraclavicular region and the right midzone. The right costophrenic angle is obscured. There is some infiltration of the left infraclavicular region and midzone at the periphery.

A bronchogram (figure 22) shows clearly that there is bronchiectasis of the right upper lobe in addition to the cavity and shows the size and drainage of the cavity in the midzone.

An artificial pneumothorax was then commenced and, on a few separate occasions, adhesions were cut. Eventually a moderately successful pneumothorax was obtained but an obliterative pleuritis developed and the pleural space was lost.

A bronchogram (figure 23), taken nearly a year after induction of pneumothorax, shows

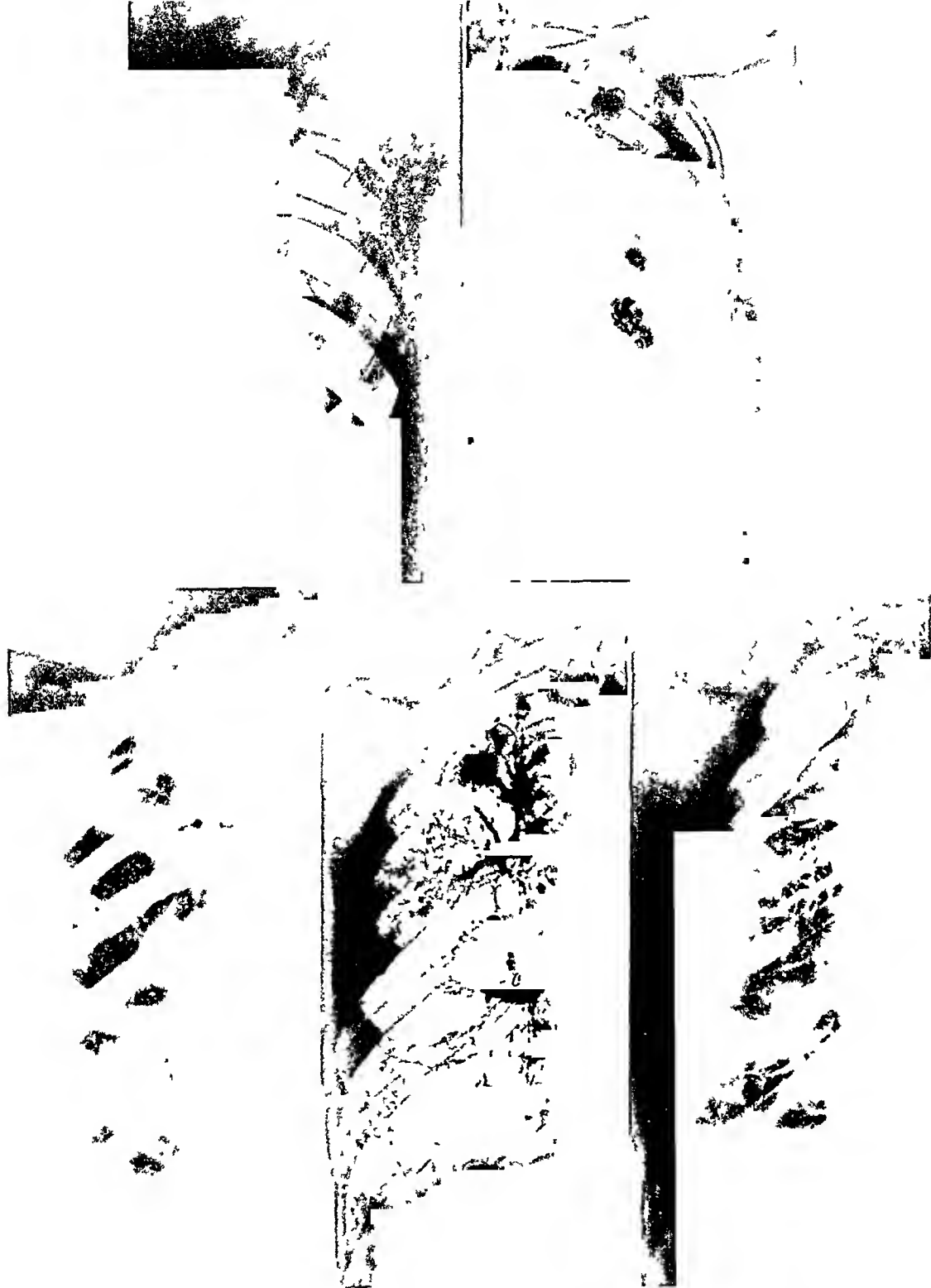


FIG 19. Upper left, FIG 20 Upper right, FIG 21 Lower left, FIG 22 Lower centre;
FIG 23 Lower right

that the two large cavities have closed, but that a residual bronchiectasis remains at the apex and at the base near the mediastinum.

This type of case will eventually result in closed cavities if a pneumothorax is effective and maintained over a long period, but the bronchiectatic areas very seldom, if ever, close permanently. It is interesting to note that this case subsequently had a thoracoplasty performed and that the sputum was still positive after the whole series of operations, spread over three years, and that the bronchiectatic areas remained even after the major operations.



FIG. 24. Left; FIG. 25. Right

Case 10: O. P., Indian male, aged twenty-three years. He has been ill for six months with cough, sputum, loss of weight and appetite, and fever. He was admitted to the hospital on account of hemoptysis. He is a thin looking Indian. Temperature is 100 to 102°F.; pulse 100 to 120. Sputum contains tubercle bacilli. The physical signs are dullness and bronchial breathing over the right upper lobe and some crepitations over the left upper lobe.

An X-ray film showed massive infiltration in the right upper lobe and a cavity in the right infraclavicular region, 2 x 2 inches. There was some infiltration in the left infraclavicular region with a small cavity $\frac{1}{2}$ x $\frac{1}{2}$ inch in this area.

An artificial pneumothorax was induced on the right side and the X-ray film (figure 24) shows an artificial pneumothorax with a large cavity in the upper lobe adherent to the periphery. The lower lobe appears normal.

A bronchogram (figure 25) shows that the main bronchus to the upper lobe is blocked. The rest of the bronchial tree shows normal alveolar filling.

The blocked bronchus in this case is due to kinking, and such cases do not respond well unless adhesions are cut to allow the kink to straighten out.

Group 6. Tension Pneumothorax

Case 11: E. 110, European male, aged twenty-two years. He has had a cough for two and one-half years. Two years ago he was admitted to the hospital for pleurisy. He was sent to a general hospital for a period of four months on two occasions and then spent six months in a sanatorium where a bilateral artificial pneumothorax was performed. He is a thin, ill looking European male. Temperature is 98 to 100°F.; pulse 80 to 120. Sputum contains tubercle bacilli. The physical signs are those associated with bilateral pneumothorax.

An X-ray film showed a bilateral pneumothorax. The left side was opaque and there was thickening of the left pleura.

A bronchogram showed extensive cavitation of the left lung.

A later X-ray film and bronchogram showed the results of tension artificial pneumothorax done in order to collapse the cavities. Pressures of plus 16 to plus 20 were registered.

The patient suddenly developed a bronchopleural fistula and the bronchogram showed the opaque medium actually entering the fistula from the pleural cavity.

Tension pneumothorax is not a wise method of treatment and this case illustrates its danger.

We feel the foregoing cases illustrate graphically the statements made in the first part of this paper.

SUMMARY

1. A brief statement is made of the effect on the lungs of artificial pneumothorax.
2. Eleven cases are described to illustrate the points mentioned. The description is illustrated by bronchograms.

SUMARIO

1. Sumarízanse en este trabajo el efecto del neumotórax terapéutico sobre los pulmones.
2. A fin de ilustrar los puntos mencionados, descríbense 11 casos con bronco-grafías que los aclaran.

REFERENCE

- (1) TANNENBERG, J., AND PINNER, M.: *J. Thoracic Surg.*, 1942, 11, 571.

ACID-FAST BACILLI IN NONTUBERCULOUS PULMONARY DISEASE¹

RICHARD A. S. CORY

Since the discovery of the tubercle bacillus by Koch (1) in 1882, it has been generally considered that the presence of acid-fast organisms in the sputum from a case of pulmonary disease indicates tuberculosis.

One is warned, however, against regarding an isolated positive finding in an otherwise atypical clinical picture as final proof of the tuberculous origin of the disease.

The average case presents relatively little difficulty, but once in a while the physician or surgeon may be confronted by a clinical condition where early accurate diagnosis is of paramount importance, but where the picture has been so obscured by the laboratory report as to render diagnosis virtually impossible before the lapse of considerable and often valuable time has taken place. The writer has been so forcibly struck by a case of this nature recently under his care, that he has decided to present the history of this case, and one other, together with the results of a brief survey of some of the standard texts on Bacteriology, Medicine and Surgery with regard to the presence of acid-fast bacilli other than tubercle bacilli in nontuberculous pulmonary lesions.

In the case in question the diagnosis lay between acute pulmonary abscess and acute tuberculous consolidation of an upper lobe with commencing cavitation. The history and clinical picture pointed unreservedly to abscess, but the laboratory reported acid-fast organisms in the sputum, together with a positive result for acid-fasts on culture of the sputum.

When the patient came under the writer's care at this stage he was so desperately ill that it was obvious that surgical drainage of the abscess—if it was an abscess—should be undertaken without delay.

But what if the case were really one of tuberculosis? Drainage of such a lesion would only court, even if it did not immediately precipitate, disaster. If however it should be an abscess and drainage were withheld, the patient would probably die within a few weeks.

The situation in such a case is so grave that the writer ventures to offer his experiences in the hope of promoting further interest in a subject which, though admittedly rare, does not seem to have received in the literature all the attention it deserves.

In the case reports brief notes on another similar case are also appended.

Case 2 however ran an acute uncomplicated course which ended in complete resolution of the lesion in so short a time as to make a diagnosis of tubercle untenable, even though the laboratory had reported the isolation by culture of acid-fast organisms from the sputum.

The discovery of the tubercle bacillus in 1882 led rapidly to the search for similar organisms and within a few years a number of them were described.

¹ From the King George V Jubilee Memorial Sanatorium, Liguanea, Jamaica, British West Indies.

Topley and Wilson (2), in what is probably the best summing up of the position with regard to the nontuberculosis acid-fast organisms, give extensive references, some of which are mentioned here.

They point out that acid-fast saprophytes have been found in water, butter, dust, grass, smegma, feces and milk. They have been isolated from the animal body but do not appear to produce disease, or at least progressive disease.

Between 1885 and 1906 a number of acid-fast organisms were isolated, and the work done showed that, though in occasional cases localized tubercle-like lesions were produced in inoculated animals, nevertheless progressive disease, such as occurs after inoculation with the tubercle bacillus, was not to be expected. The bacilli are essentially saprophytic with occasional localized toxic action.

When injected intraperitoneally in large doses, particularly when mixed with a fat, like butter, they may give rise to lesions closely resembling tubercle. These lesions are considered by Topley and Wilson to be most probably due to lymphatic and leucocytic dissemination with resultant focal reactions. Nodule formation and even caseation have been seen to occur and acid-fast bacilli have been recovered from such lesions.

After subcutaneous or intramuscular injection, however, the lesions are confined to the site of the injection and the regional lymph nodes, and further dissemination is not observed. Cultures made from the recovered bacilli show a growth in a very few days, as against the longer period required by the tubercle bacillus, and further guinea pig inoculation with saline suspensions of these cultures is harmless.

In a discussion of the pathology of the lesions produced by these organisms Topley and Wilson, quoting Rabinowitsch (1897)(2a), state that they are more exudative than proliferative, and that there is less tendency to caseate than is observed in tuberculous disease. Polymorphonuclear cells are more common than epithelioid cells and typical giant cells are rare.

These authors also point out that intravenous inoculation of the bacilli, either living or dead, into laboratory animals causes severe illness and sometimes death. As the living bacilli do not appear to multiply in the tissues, the effects are presumably due to a toxemia from liberation of an endotoxin.

Acid-fast saprophytes have been isolated from a number of human tissues and exudates and a consideration of lung lesions should bear this in mind.

In 1900 Rabinowitsch (2b) isolated them from cultures of a gangrenous lung, while in the same year Marzowsky (2c) reported finding them in the tonsils. In the following year (1901) Mironescu (2d) found them in human feces and Karlinsky (2e) in nasal secretions. In 1931 Beavan and Bayne-Jones (2f) reported them in a specimen of pleural fluid, and Tiedemann (2g) in blood. They were found in pus in 1933 by Bruynoghe and Adant (2h) and the same year Cummins and Williams (2i) described their discovery of them in sputum.

Some of these findings, such as those concerning the gangrenous lung, the pleural effusion and the sputum, are of considerable interest to the internist and chest surgeon.

The fact emerges that acid-fast saprophytic organisms are extremely common

and wide-spread in nature and can appear in lesions in man, even though they have probably played no real part in the causation of such lesions.

It should not be forgotten, however, that at least some of the reported discoveries may have had their origin in dust or tap-water contamination of the tissues or exudates studied.

Ford (3), in his text-book, mentions the relative ease with which organisms of this group will grow on culture media, as well as the pathogenic action on intra-peritoneal inoculation into guinea pigs of the butter bacillus (*Myco. butyricum*, isolated by Rabinowitsch in 1897 from some butter in Germany).

The timothy grass bacillus (*Myco. phlei* I) and the mist bacillus (*Myco. stercoris*) also appear to possess this pathogenic action for guinea pigs.

Like Topley and Wilson, Ford describes the resultant lesions as very similar in some respects to those produced by the tubercle bacillus.

Hewlett (4), in his Manual of Bacteriology, makes but scanty reference to the acid-fast saprophytes but generally confirms the findings already discussed.

Baldwin, Petroff and Gardner (5) call attention to errors that may arise in laboratory diagnosis on account of the possible presence of acid-fast organisms in the tap water used in laboratories or even in distilled water that has been left exposed to the air. They suggest that such organisms are really grass bacilli derived from the dust of hay.

Norris and Landis (6) in the discussion on pulmonary gangrene in their famous text-book on chest diseases point out that acid-fast organisms have been reported in the pus in several cases of pulmonary gangrene. The work which they quote, that of Ophuls published in 1902, is in line with that already mentioned as having been carried out by Rabinowitsch in 1900, and should be regarded as of some importance.

Powell and Hartley (7) also quote Ophul's work on *Acid Proof Bacilli in Five Cases of Pulmonary Gangrene* published in the Journal of Medical Research, and they suggest that in some cases these organisms may be responsible for at least a part of the pathological changes observed in such lesions in the lungs.

They do not, however, lay much stress on the diagnostic difficulties that these findings may occasion.

Graham, Singer and Ballou (8) make no mention of the possible presence of acid-fast bacilli in the sputum of either lung abscess or bronchiectasis, nor do such organisms appear to have been found in the cases occurring in their clinic and reviewed in the book, in spite of careful and very full bacteriological studies.

Davidson (9) in a more recent work likewise makes no mention of the occurrence of acid-fast organisms in nontuberculous pulmonary disease, nor does Sellors (10) mention them in his book on Surgery of the Thorax.

Price (11) only makes casual reference to acid-fast organisms, which he classes as *Streptothricae*, in connection with lung gangrene. Their possible occurrence in abscess or bronchiectasis is not listed.

Cecil's Text Book of Medicine (12) touches on Ophul's previously mentioned report in lung gangrene but lays no emphasis upon it and does not refer to either abscess of the lung or bronchiectasis in this connection.

Poulton (13) has nothing to say upon the subject, nor has Beaumont (14) in a very recent book on general medicine. Of the texts on general surgery only Christopher (15) and Howard (16) have been consulted, and neither of them mentions the matter.

From this survey of some of the standard works on general medicine and surgery it will be seen that the presence of nonpathogenic acid-fast organisms as a stumbling block in the diagnosis of chest lesions is not considered to be of much importance.

Review of some of the more important books on pulmonary tuberculosis reveals a rather greater interest in the matter, but current texts still fail to lay much emphasis upon these organisms as the possible cause of serious mistakes.

Burrell (17) makes no mention of them at all. The book, however, is only a short one and, as its name implies, is concerned largely with the advances in tuberculosis work up to 1931.

Wingfield (18) mentions the fact that certain very rare pathogenic streptothricae have acid-fast properties, but suggests that for practical purposes these, as well as the better known acid-fast saprophytes, will not be likely to cause confusion in the examination of pathologic tissues or exudates. He also reminds us that some of the segments of certain varieties of actinomyces may exhibit acid-fast properties.

In Goldberg's *Clinical Tuberculosis* (19) Mellon says of the acid-fast saprophytes "... even when found inside (the animal body) their existence is a commensal one, never being known to have given rise to disease."

In the section on laboratory diagnosis in the same book, Koch and Mellon make no mention of the presence of acid-fast saprophytes in the sputum as a possible cause of diagnostic confusion.

Kane, Pagel and O'Shaughnessy (20) go rather more thoroughly into the matter and call attention to a smooth growing saprophyte that may occur in the human body, while they also point out that acid-fast saprophytes may sometimes be found in the lymph nodes of normal guinea pigs, an obvious and quite possible source of error.

Like some of the previously mentioned writers they warn that contamination of a microscopic preparation by these organisms is possible, particularly as they sometimes occur in tap water.

Acid-fasts other than tubercle bacilli may be present in material, such as urine, sent for examination, but of the sputum they say "... it is generally recognised that an acid-fast bacillus in the sputum is tantamount to a tubercle bacillus."

Mention however is made of recently reported cases (Cummins and Williams, and Baldwin) where acid-fast bacilli, not tubercle bacilli, have been found in lung lesions which closely simulated phthisis.

Perhaps the best note in regard to this subject is by Ustvedt (21) in his recent little book *Pulmonary Tuberculosis*. He stresses the importance of guinea pig inoculation as the final court of appeal in the diagnosis of pulmonary tuberculosis, pointing out that saprophytic acid-fast bacilli not uncommonly occur in different parts of the body such as the oral cavity and tonsils, while in path-

ologic conditions of the lung, such as bronchiectasis and gangrene, they may be found in the purulent sputum. In addition to the above he remarks that by growing on the culture media used for tubercle bacilli these organisms may still further confuse the issue.

In a recent article on dermoid cysts of the mediastinum, Rusby (22) gives an account of a case where such a cyst, obstructing a bronchus by pressure, had given rise to bronchiectasis in the distal segment of lung. The sputum from this area of infection was found to contain clumps of acid-fast organisms and was first reported as positive for tubercle bacilli. Further study, however, revealed that the organisms, though acid-fast, were not alcohol-fast. Rusby adds that he was unable to find in the literature any mention of a similar case where acid-fast but non-alcohol-fast organisms were found in the sputum. In the 2 cases reported here the acid-alcohol technique was used in the staining of the microscopic preparations.

In these 2 cases which have come to the writer's attention within the last year we have an excellent illustration of one of the occasional diagnostic pitfalls. It must be remembered, however, that they are relatively uncommon, and the thought that "everything that is acid-fast in a sputum is not necessarily a tubercle bacillus" should not be allowed to obtrude itself too markedly in clear-cut cases, but should be kept in mind when dealing with others where the diagnosis is not so certain.

CASE REPORTS

Case 1: The patient was a male, white, police officer, 29 years of age, who, until the illness here reported, had been in first-class physical condition, and an enthusiastic football player.

On September 20, 1943 he had had a lower right molar tooth extracted. On September 22 he noticed slight swelling of the side of the neck as well as a little difficulty in swallowing. By September 24 the swelling had enormously increased, and the temperature had risen to 103°F. On that date he was admitted to the Kingston Public General Hospital and a small incision was made into the floor of the mouth below the tongue. No free drainage was obtained and the next day (September 25) multiple incisions were made around the neck below the jaw. Large amounts of stinking pus freely mixed with gas escaped and by the next day (September 26) he felt much better. Bacteriological study of the pus was not undertaken, but intensive treatment with sulfonamides and antigasgangrene serum was given. Temperature, however, remained elevated and respiratory distress set in and on September 29 a tracheotomy was done. This, together with oxygen, eased the acute condition, but within forty-eight hours an irritating nonproductive cough had started.

A chest X-ray film on September 28 showed a generalized increase of lung markings with hazing in the left cardiophrenic angle. Cough continued and another film on October 12 showed some hazing of the mesial portion of the right upper lobe with a general clearing of the previously increased markings.

Sputum examinations by concentrations on October 13 and October 18 were negative for tubercle bacilli, but an examination on October 20 showed a few suspicious acid-fast rods and a culture for tubercle bacilli was then set up.

On November 4, 1943 the patient was discharged at his own request, relatively afebrile, but still coughing and raising a certain amount of mucoid sputum. The gas infection had

been controlled and the wounds were healing. The tracheotomy tube had been removed and this wound was also healing well. He rested at home, and for a week in a nursing home, until November 29 when he had a severe bout of coughing which resulted in the sudden expectoration of about 5 or 6 ounces of stinking pus. When this occurred he had been febrile again for two or three days with temperature ranging from 100° to 102°F.

Cough now became intense, and he was quite unable to obtain any rest except when sitting bolt upright in a chair.

On December 3 the sputum culture which had been set up on October 20 for tubercle bacilli was reported as being positive, and the patient was referred to the Tuberculosis Clinic from which institution he was sent for admission to this hospital on December 5, 1943.

The writer's first contact with the patient was on the day of his admission when the following note was made on his clinical records: "The history here is absolutely typical of lung abscess, but one is considerably shaken by a positive sputum culture. The two conditions may coexist, but I feel that the main pathology is septic infection of the lung and not tubercle."

Physical examination revealed a desperately ill man weighing 120 lbs. as against his normal of 165 lbs. He coughed incessantly and sat with his head downwards and his chin almost on his chest. He was highly febrile; the temperature was swinging 2 to 3 degrees a day. There was pain and some tenderness over the upper lobe of the right lung, more particularly high in the right axilla.

Examination of the lungs revealed signs of a dense lesion in the right upper one-third, though there were relatively few râles. There were no other abnormal signs in the chest.

The heart and abdomen were essentially normal and, though he was extremely irritable and not very coöperative, there was no evidence of organic disease of the central nervous system.

Blood studies revealed a high sedimentation rate—35 mm. by the Cutler method after one hour, together with only a slight increase of leucocytes (10,300) with 68 per cent polymorphonuclear cells. Hemoglobin was 72 per cent. The Kahn test was negative and urinalysis revealed no abnormality.

An X-ray film of his chest showed a dense consolidation in the upper lobe with irregular central excavations. The right lower half was relatively normal, as was also the left lung.

Daily sputum examinations during the first week after admission, both by smear and concentration, were all negative for tubercle bacilli. No spirochetes or fusiforms were found in the sputum, nor were amebic cysts present in it.

The difficulty lay in knowing what to do next.

If the condition was a lung abscess as indicated by the history and clinical condition, open drainage was an urgent necessity. If, on the other hand, it was tuberculosis, as indicated by the reported positive sputum culture, drainage would do more harm than good. The two conditions might even coexist. Bronchoscopy was decided against on account of the neck rigidity, as it would have required a general anesthetic, and in any case would probably only have confirmed the fact that pus was coming from the right upper lobe.

It was finally decided to deal with the case by open operation as most of the clinical evidence was in favor of lung abscess, while the history was absolutely typical.

Lateral X-ray views showed the cavity in the midaxillary area, probably in the posterior portion of the axillary segment of the upper lobe. A one-stage operation through the bed of the second rib was planned. The operation was done on December 13, 1943 (eight days after admission).

Anesthesia consisted of a small preliminary dose of 5 per cent pentothal intravenously, and was carried on by open ether after the introduction of an intratracheal catheter for suction. Three inches of the second rib in its central section were removed and the pleura was found satisfactorily adherent. Abscess cavity was located immediately below the exposed area with an exploring needle at a depth of about three-quarters of an inch, and was laid open and packed with acriflavine gauze.

The abscess consisted of a biloculated cavity, as was suggested by the X-ray appearance, and was about as large as a golf ball.

Large quantities of pus were aspirated through the tracheal catheter both during and immediately after the operation, and the patient left the theatre in good condition; 450 cc. of blood plasma were given after his return to his room.

The pack was removed two days later under pentothal anesthesia, and from this time until the final operation it was changed every second day under pentothal.

Improvement was rapid and the cough quickly diminished, though he needed morphine and codein for several weeks in order to ensure rest, as he complained of a great deal of pain.

The day of the operation some of the sputum was inoculated into a guinea pig and autopsy of the animal on January 26, 1944 showed no evidence of tuberculous lesions. Culture of the same specimen was returned negative on February 14, 1944.

The patient's condition continued to improve until January 11, 1944 when an acute inflammation of the right side of the neck developed. It had the appearance of an erysipelas and sulfathiazole was administered with improvement.

A week later a small abscess appeared on the left side of the neck near one of the old scars and this was opened. By January 26, 1944 the right side of the neck was again acutely inflamed and fluctuating. By this time the opening into the pulmonary cavity had closed down so much as to make packing very difficult and it had to be enlarged. This was done, and a section of the third rib was removed at the same time. The neck was freely opened on both sides and some pus with caseous looking material was evacuated. This pus was cultured both for ordinary septic organisms, for which it was sterile, as well as for tubercle bacilli. Anaerobes were not sought for. The culture for tubercle bacilli gave a growth of acid-fast organisms on March 9, 1944, and these organisms were then inoculated into a guinea pig. The colonies of these bacilli were yellow to yellowish-brown.

On April 14, 1944 tuberculin test on the pig was doubtful, and on April 24 it died and was autopsied. Sections of the liver, spleen, lungs, lymph nodes and tissues at the site of inoculation were examined microscopically. The pathologist's report on the examinations was as follows:

"In the tissue from the site of injection there is inflammatory reaction and tissue necrosis, and acid-fast organisms (rods) are present. One of the glands shows central necrosis, but histologically none of the other tissues submitted show any infection suggestive of tuberculosis."

By the end of February, 1944, namely about four weeks after they were opened, the neck wounds were firmly healed, and all inflammatory reaction in this area had subsided. This is in very striking contrast to what one would expect with tuberculous disease.

On March 3, 1944 the opening into the lung, which had again contracted, had to be reopened. During all this time, however, the patient had been steadily improving and he gained some 30 pounds in weight, was afebrile and had very little cough and a negligible amount of sputum.

By April 14, 1944 the abscess cavity was clean enough for closure with a muscle graft.

On this date the final operation was done using a pedicle graft of pectoralis major to fill the deficiency in the lung. Healing took place by primary intention and the patient was discharged to his home on April 22, 1944, that is, approximately four and one-half months after the initial operation. He returned to work in June, 1944 and has kept well since.

Case 2: This case is reminiscent of case 1 except that here the disease resolved rapidly and completely on its own, and did not progress to cavitation needing surgical treatment.

The patient, a colored female, 33 years of age, was admitted to the Kingston Public General Hospital on January 3, 1944 with an acute febrile illness with cough, and râles in the right upper third. Chest X-ray film on January 5, 1944 showed a pneumonic type of lesion in the lower zone of the right upper lobe. The sputum was twice negative for tubercle bacilli on concentration, but culture set up at the same time for tubercle bacilli was returned positive on February 21, 1944.

Before this, however, the fever had rapidly settled, and an X-ray film on January 18, 1944, that is, thirteen days after the initial film, showed very marked clearing of the lesion.

By February 25 clearing was complete and the patient has remained well and free from symptoms ever since.

Follow-up X-ray examination in May, 1944 shows no trace of the original lesion.

Guinea pig inoculation of the material in this case was never done. As the patient is now well, there seems no likelihood of another specimen being obtainable for further study.

It is to be regretted that no attempt was made to carry out further studies with regard to morphological or cultural characteristics on the organisms isolated from these 2 cases. One is not, therefore, in a position to differentiate between avirulent tubercle bacilli and saprophytes.

Microscopically there was nothing whatever to distinguish them from tubercle bacilli, and the times taken for growths to appear on the culture media rather suggested that they were different from the ordinary acid-fast saprophytes which normally grow easily and quickly, often being apparent in a few days.

In case 1 the original culture of sputum showed a growth in the sixth week, while the culture of the pus obtained from the neck lesion showed a growth in the fifth week. In case 2 the sputum culture gave a growth in the fifth week.

It is possibly of interest to record that all positive growths were obtained on Loewenstein-Jensen's medium or on that of Petragnani, while no growth was obtained in either case using the same material on Petroff's medium.

This is in keeping with the findings of Koch and Mellon (19) for tubercle bacilli.

SUMMARY AND CONCLUSIONS

The occurrence in nature of saprophytic acid-fast organisms is discussed and, in this connection, a review of some of the standard texts on pulmonary disease is given.

These organisms occurring in cases of nontuberculous lung disease may so confuse the issue as to make the diagnosis difficult until the necessary time has been taken to work out the pathogenicity for laboratory animals of the organisms found.

Such delay may occasion grave danger, and perhaps even disaster to a patient under consideration for treatment. At another time such a patient may be tagged with a diagnosis of tuberculosis, which may follow him for the rest of his life and may possibly lead to lengthy and costly treatment in a sanatorium or hospital.

Two cases are reported where the sputum was returned positive on culture for tubercle bacilli, but where the clinical course of the conditions was of a nature to throw considerable doubt upon the laboratory findings.

The first patient suffered from a fetid abscess of the lung, and the acid-fast organisms found in the tissues were proved by animal inoculation to be non-pathogenic. The second case, one of an atypical pneumonitis, resolved so rapidly and completely as to render the diagnosis of tuberculosis untenable, in spite of the report of a positive culture of the sputum.

In conclusion the writer would urge a more critical attitude towards the results of positive cultures on otherwise atypical cases, unless these results are backed up by definitely positive findings as a result of animal inoculation.

SUMARIO Y CONCLUSIONES

Discútese la existencia en la naturaleza de microbios ácidosresistentes saprófitos y repásase lo dicho sobre la materia en algunos de los tratados de neumopatías mejor conocidos.

En los casos de neumopatía no tuberculosa la presencia de estos microbios puede enredar el problema a tal punto que dificulte el diagnóstico hasta que se dedique el tiempo necesario a dilucidar la patogenicidad de los gérmenes presentes para los animales de experimentación.

Esa tardanza puede suscitar un peligro grave y quizás hasta resultaría desastroso para un enfermo cuyo tratamiento esté en estudio. Otras veces uno de estos enfermos puede ser rotulado con un diagnóstico de tuberculosis que lo siga todo el resto de su vida y posiblemente motive un tratamiento prolongado y costoso en un sanatorio u hospital.

Comunicanse dos casos en los que el esputo fué considerado positivo al hacer cultivos en busca de bacilos tuberculosos, pero en los que la evolución clínica fué de tal naturaleza que puso en tela de juicio los hallazgos del laboratorio.

El primer enfermo padecía de absceso fétido del pulmón y los microbios ácidosresistentes descubiertos en los tejidos resultaron anapatógenos al ser inoculados en animales. El otro caso, de neumonitis atípica, mostró una resolución tan rápida y completa que desvirtuó el diagnóstico de tuberculosis a pesar de ser positivo el informe del cultivo del esputo.

Al terminar, el autor recomienda una actitud más crítica hacia los informes de cultivos positivos en casos atípicos en otros sentidos, a menos que sean reforzados por hallazgos definitivamente positivos basados en la inoculación en animales.

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INCIDENCE OF TUBERCULOSIS IN JAPANESE-AMERICANS¹

A Study of a Homogeneous Racial Group

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Among the various factors influencing the morbidity of tuberculosis, such as age, occupation, economic conditions, etc., is that of race. Statistical studies seem to indicate that the colored races generally show a tendency for increased tuberculosis morbidity rates, and these in turn are reflected by increased mortality rates. Thus, in this country, in 1932, the mortality from tuberculosis varied from 32 per 100,000 population to 155, in a survey of 46 cities. The figures for the white population varied from 21 to 158, whereas the figures for the Negro population ranged from 49 to 797 (1).

This higher figure for Negroes is not very far removed from those tabulated for the other colored races. Thus the following rates for pulmonary tuberculosis are quoted in a report of the Health Organization of the League of Nations for 1933-1934: Bombay—140, Madras—146, Calcutta—217, Singapore—253, Manila—479 and Tokio—279 (1).

Shortly after the attack by Japan upon Pearl Harbor, a mass evacuation of persons of Japanese ancestry occurred on the Pacific Coast, as ordered by the U. S. Army. These evacuees, numbering approximately 110,000 persons, were removed to various Relocation Centres situated for the most part in the Western States. Under the administration of the War Relocation Authority, a war agency, they were formed into colonies of from 5,000 to 15,000 population. An effort was made to keep families intact and in the various colonies this was carried out for the most part, so that families of 5 or less persons occupied living quarters in buildings of the barracks type. To each colony was attached a Base Hospital with clinic and Public Health facilities.

This report covers a tuberculosis survey conducted among 2,771 employees, all of Japanese ancestry, and thus constituting a homogeneous racial group, at the Tule Lake Relocation Centre (now the Tule Lake Segregation Centre), Newell, California. The evacuees at this centre were principally from the States of California, Washington and Oregon and represented a cross-section of both an urban and agricultural population. At the time of this survey, they had been living in the centre from six to ten months.

The group examined therefore was the equivalent of a random adult population sample from the aforementioned states and was unselected as to previous home environment, economic status, etcetera.

A few words concerning the attitude of the Japanese people toward tuberculosis is appropriate at this point.

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This group, as is the case among Japanese people as a whole, accepted tuberculin testing with approval, regarding it in the same light as vaccination against smallpox or any other such prophylactic health measure. There was a certain amount of reluctance, however, to submit to fluoroscopy and an even greater reluctance to submit to X-ray examination, as these methods were more clearly identified as case-finding procedures. An extreme reluctance was encountered in the acceptance of the diagnosis of tuberculosis, even in the arrested cases, since the disease in any form is a social stigma which attaches itself to the family. The stigma is particularly unfortunate in the case of contemplated marriage, since the families concerned in many instances will make extensive inquiries reaching back several generations regarding each other. These inquiries take in the question of mental ailments and leprosy, as well as tuberculosis and it has not been unusual for Japanese in this country to write to Japan for information of this type. This social stigma of tuberculosis is based upon the false conception that the disease is inherited, and this conception is more prevalent among the parents. The second generation Japanese is more apt, however, to have a correct knowledge of the pathogenesis of tuberculosis and in such instances may risk parental displeasure or even ostracism by marrying into a family in which there is a history of tuberculosis.

METHOD OF SURVEY

The survey was conducted among an unselected late adolescent and adult population group, consisting of food handlers, hospital employees, hog farm and farm lunch crew, members of the fire department, as well as a miscellaneous group of evacuees who voluntarily presented themselves for tuberculin testing.

Old Tuberculin in dilution of 1:10,000 was given in the routine manner and readings made twenty-four and forty-eight hours after the injection. A positive reading at either time was considered as a positive test and all persons having such positive tests were fluoroscoped.

Fluoroscopy instead of routine radiographic examination was done in these cases because of budgetary reasons. At the same time it was desired to correlate fluoroscopic and radiographic findings to determine the advisability of the use of fluoroscopy as a method of case-finding where routine radiographic examination was not feasible.

Fluoroscopy was done by one person with proper accommodation so as to eliminate the personal factor as far as possible. Any variation from the normal, including the presence of a healed primary complex, was followed by routine radiographic examination. Radiographic results were divided into the following categories:

1. Cases not in need of further supervision
 - a. Negative.
 - b. Healed primary complex.
 - c. Healed pleural effusion; no clinical history.
2. Cases in need of further supervision
 - a. Active cases.

- b. Apparently arrested cases, with or without previous clinical history, age below 40 and quiescent cases.
- c. Apparently cured reinfection type, age over 40 and lesions of the minimal fibro-calcific type.

RESULTS

A total of 2,771 persons received tuberculin tests; 1,389 were males and 1,382 were females, practically an equal distribution of the sexes. Of these, 1,233 tests were positive, or about 45 per cent of the group.

Almost all reactors were fluoroscoped (1,216); of these, it was necessary to take X-ray films of 84 persons.

The radiographic results can be summarized as follows:

1. Cases not in need of further supervision: 39 cases were of this type. One case of neurofibroma was found and was included in this group.
2. Cases in need of further supervision: tuberculous cases; 45 (3.69 per cent) cases were found in this group which showed the following subdivisions:
 - a. Active cases: 5 (.41 per cent)
 - b. Arrested cases: 32 (2.62 per cent)
 - c. Apparently cured: 8 (.66 per cent)

Analysis of results: The problem of tuberculosis in the Oriental races, and particularly the Japanese, has been investigated by Dickey (2). This study was carried out in San Francisco, before the present war, and was conducted among a group of both Chinese and Japanese children of all ages, who were subjected to tuberculin testing and X-ray studies. Positive tuberculin tests were found in 35.3 per cent, the incidence for Japanese children being 38.5 per cent. In a later study (3) the same author found positive reactions in 60 per cent of the age group 12 to 14 in Japanese children, a higher figure than that for similar groups taken from the child population at large.

Our results showed 1,233 positive tuberculin reactions, or 45 per cent, a figure which compares more closely with that of 46.6 per cent found in children 14 to 15 years of age in the general population in San Francisco, in the years 1925 to 1928 (4). Since our group was an adult one, the figure obtained (45 per cent) is actually smaller than would be expected from an older population. This discrepancy might be attributed to the presence of persons from rural communities in the group of this investigation. However, it is to be remembered that these persons lived for a considerable period in somewhat crowded conditions in the centre.

The incidence of tuberculosis in the present study was 3.69 per cent, a figure which was higher than that reported in 1931 for Japanese in San Francisco in a nine-month period (1.2 per cent). However, the incidence in our study was smaller than that reported by Swartout and Dierker (5) for native white Americans of Los Angeles County, California, who reported the results of a routine X-ray survey of 1,634 food handlers. They found 97 cases requiring supervision (6 per cent as compared to our 3.69 per cent), of which 7 cases (0.43 per

cent) were active. This latter figure may be compared with the percentage of 0.41 active cases found in this group.

In summarizing, this study shows a percentage of positive tuberculin tests comparable to those of other population groups in this country. At the same time, the incidence of pulmonary tuberculosis on radiographic study was found to be no higher than has been reported for unselected persons of the white race in California, although it must be pointed out that a more wide-spread use of X-ray films instead of fluoroscopy would undoubtedly have revealed some additional cases with minimal lesions.

This incidence is not surprising in view of the decreasing death rate from tuberculosis in San Francisco among the Japanese for the past twenty years, from a high of 474 in 1919, to 42.73 for 1939 and 70.45 for 1940 (1).

Coincidental with this must be borne in mind such factors as second generation adaptation to American conditions and the educational campaign for better personal hygiene, better housing, etcetera.

Of great importance has been the gradually increasing eradication of the conception of tuberculosis as a social stigma and its replacement by an understanding of the pathogenesis of the disease and the value of early diagnosis and treatment. Yet, the question of social stigma probably remains the most serious and difficult problem in dealing adequately with the discovery, treatment, and the subsequent rehabilitation of persons of Japanese ancestry.

CONCLUSIONS

1. A study of the incidence of tuberculosis in a homogeneous racial group of Japanese-Americans is presented.
2. Fluoroscopy has been demonstrated as a valuable adjunct in case-finding, when routine radiography is not feasible.
3. The incidence of pulmonary tuberculosis in the group herein reported is no higher than that of similar groups of native Americans from the same geographical area.

CONCLUSIONES

1. Preséntase un estudio de la incidencia de la tuberculosis en un grupo étnico homogéneo de japoneses-americanos.
2. Queda aquí demostrado que la roentgenoscopia constituye un valioso coadyuvante en el descubrimiento de los casos, cuando no puede emplearse la radiografía sistemática.
3. En el grupo descubierto la incidencia de la tuberculosis pulmonar no fué mayor que en grupos semejantes de naturales de Estados Unidos procedentes de la misma zona geográfica.

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TUBERCULOSIS SURVEY OF FOOD HANDLERS ON THE ISLAND OF OAHU

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In the Territory of Hawaii, health department regulations had directed that every employer shall require of each of his employees, who in the course of his employment comes in contact with foodstuffs, a physical examination at least once each year. The employee was required to present to his employer annually a certificate from a licensed physician, on a form approved by the Board of Health, showing that the employee was free from all infectious or contagious diseases. The health department form contained a minimum of information, and laboratory studies were to be carried out only upon the recommendation of the examining physician. It was the consensus of most physicians and health workers that this examination did not protect the public health to the extent that the expenditure and time involved by this requirement warranted. Since 1936 and up to August, 1943, these requirements were followed. The public health value received did not justify the continuance of this examination; during the seven years in which 10,000 to 12,000 food handlers on Oahu were examined yearly, only 8 persons were rejected as having a communicable disease.

Because of this, the old regulations pertaining to the examination of food handlers were amended and on August 21, 1943 a new regulation was passed permitting the Board of Health to require an X-ray of the chest of all food handlers. From time to time and as often as deemed advisable for the protection of the public health, any food handler or class of food handlers is to be examined by a physician designated by the Board for the purpose of determining the presence or absence of active tuberculosis.

The new regulation was prepared because it was felt that the former regulation was not comprehensive enough to justify the expense and effort of the private physicians and the Board of Health. Also, many of the examinations previously carried out were not thorough enough to provide satisfactory protection of both the food handler and the public. The chief change effected by the new regulation is that the emphasis is now placed on the discovery of tuberculosis among food handlers. It also places greater emphasis on the individual responsibility of the employer and employee in preventing the transmission of any communicable disease.

In addition to the above reasons, records available at the local tuberculosis sanatorium showed 15 per cent of the patients to be food handlers. Approximately 17 per cent of the 1,700 cases of tuberculosis carried on the active register are or had been engaged in handling food. Records at the Honolulu Chest Clinic of the Bureau of Tuberculosis also showed the incidence of tuberculosis to be approximately fifteen times higher in this group than in other occupations.

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The sudden increase in civilian and military personnel throughout the islands, with the accompanying housing shortage, crowded and inadequate living conditions, and the increased demand for services of the eating establishments, called for active measures in tuberculosis case-finding.

METHOD OF SCHEDULING THE FOOD HANDLERS

With the coöperation of the Bureau of Sanitation, the sanitary inspectors carried out a uniform method of scheduling food handlers for visits to the mobile X-ray unit of the Board of Health. The city of Honolulu is divided into three sanitary districts for purposes of administration and supervision, and each of these districts has food inspectors to carry on all inspectional services related to food handling establishments. These inspectors have detailed knowledge of all the food handling establishments in their districts and the number of personnel in each establishment. All were directed to work out in detail with the employers a schedule for the food handlers to report for X-ray examination with a minimum of disruption of the services of their establishments. Not more than 200 to 250 persons per day were scheduled and every effort was made to have the schedule followed as closely as possible.

A blood test for syphilis was offered to each food handler X-rayed by the health department unit and about 90 per cent of the food handlers were accommodated. Health education literature was given to each food handler. A leaflet *Why X-ray* was prepared and distributed by the Tuberculosis Association of Hawaii. The Venereal Disease Division of the Board of Health also distributed leaflets on syphilis.

The personnel conducting the survey consisted of one X-ray technician, two nurses, two clerks and one voluntary helper. Administrative direction was rendered when necessary by the health department and by the Tuberculosis Association staff.

USE OF THE 4" x 5" FLUOROGRAM

Facilities were provided by the Board of Health to enable each food handler to obtain an X-ray examination. Those who could go to their private physicians or private X-ray laboratories were urged to do so. Approximately 2,500 of the 15,000 food handlers X-rayed in this survey on Oahu obtained this service privately. However, all X-ray films were reviewed by the Bureau of Tuberculosis, Board of Health. A mobile unit which contained a 200 milliamperé X-ray machine with a 4" x 5" photofluorographic attachment was used by the health department. Due to its mobility, it rendered services to the outlying districts without loss of time for the food handlers in the rural areas. The fluorograms were found to be very satisfactory and easily read. They also have an advantage in being easily handled and filed.

The 4" x 5" fluorograms were read with the following terminology to facilitate unity in readings: (1) Doubtful; (2) Suspicious; (3) Characteristic; (4) Undiagnostic; (5) Primary healed; and (6) Negative.

A 14" x 17" film was ordered for all doubtful, suspicious and characteristic 4" x 5" films. If the term undiagnostic was used, a 4" x 5" film was repeated or a 14" x 17" film was ordered, depending on the discretion of the physician reading the first film. In most of the 4" x 5" fluorograms that were undiagnostic, the reason was usually due to persons with thick walled chests or, in rural Oahu, was due to a drop in line voltage.

PROCEDURE FOLLOWING READING OF 4" x 5" FLUOROGRAMS

Persons having a negative reading received a certificate by mail, which has served as a permanent record. Instructions to the food handlers required that this record be carried and produced by the food handlers whenever requested to do so by an agent of the Board of Health.

Persons requiring 14" x 17" X-ray films were notified to report for this examination to their private physicians, private X-ray laboratories or at designated X-ray stations, which were reimbursed for the films taken. After the 14" x 17" films had been read and the doubtful cases ruled out, the other persons who had a questionable or suspicious film (14" x 17") were required to report to the Honolulu Chest Clinic for the first follow-up by a staff physician. After the first visit and examination, food handlers who could go to their private physicians for treatment and follow-up were encouraged to do so. A statement was placed on the certificate indicating the time a food handler could work before being examined again.

A guide was set up by the Chest Clinic to aid the staff physician or private physician in the follow-up of persons with characteristic or suspicious X-ray films. Patients found to have moderately advanced or far advanced lesions or cavitations were considered to have active infectious tuberculosis until proved otherwise. They were immediately excluded from food handling and hospitalized.

Persons whose X-ray films showed lesions of minimal extent were studied carefully to determine whether the lesion was (1) active or potentially active, (2) inactive, or (3) of doubtful activity. A person with definitely active lesions or lesion was excluded from food handling and recommended for hospitalization. Those found to be inactive were allowed to continue to work but were advised to return for examination at intervals of three to twelve months, depending on individual circumstances. Persons who were considered probably inactive but were thought to need further study were allowed to continue work during a period of observation, during which serial X-ray films, sputum or gastric studies and clinical examinations were required at monthly intervals until the status of the lesion was determined.

Follow-up of those persons who were permitted to continue their occupation as food handlers has been closely carried out by the Bureau of Tuberculosis, with the coöperation of the sanitary inspectors. The Bureau of Sanitation receives notices from the Tuberculosis Bureau to make the follow-up effective.

In table 1 over 314 persons, or 3.14 per cent of the food handlers, had char-

TABLE 1

*Analysis of 4" x 5" X-ray diagnosis of 10,000 food handlers**

DIAGNOSIS	NUMBER	PERCENTAGE
Minimal.....	43	0.43
Moderately advanced.....	33	0.33
Advanced.....	4	0.04
Healed and partially healed.....	234	2.34
Suspicious.....	223	2.23
Doubtful.....	42	0.42
Negative.....	8,920	89.20
Heart.....	116	1.16
Undiagnostic.....	359	3.59
Cervical rib and other rib condition.....	26	0.26
Total.....	10,000	100.00

* Only the first 10,000 of the approximate 15,000 food handlers in the City and County of Honolulu were studied in this survey.

TABLE 2

Analysis of 4" x 5" X-ray films by race and diagnosis of 10,000 food handlers

RACE	MIN.	MOD. ADV.	ADV.	HEALED	SUSP.	DOUBT.	NEG.	HEART	UNDIAG.	RIB	TOTAL
Hawaiian.....	1	0	0	2	4	1	107	2	6	0	123
Part-Hawaiian....	1	0	0	8	9	1	471	5	13	0	508
Caucasian.....	3	2	1	30	15	4	964	9	30	2	1,060
Chinese.....	11	9	1	22	42	7	1,357	25	47	0	1,521
Japanese.....	25	21	2	155	132	24	5,172	58	235	23	5,847
Filipino.....	1	0	0	12	18	4	659	15	20	1	730
Korean.....	1	1	0	4	2	1	112	0	5	0	126
Puerto Rican.....	0	0	0	1	1	0	78	2	3	0	85
Total.....	43	33	4	234	223	42	8,920	116	359	26	10,000

TABLE 3

Comparison of 4" x 5" fluorograms with 14" x 17" films in 381 persons with doubtful, suspicious, characteristic and undiagnostic findings

	4" x 5"	14" x 17"	
		Negative	Positive
Doubtful (42).....	38	9	29
Suspicious (223).....	227	51	176
*Characteristic (314).....	92	2	90
Undiagnostic (359).....	24	8	16
Total.....	381	70	311

* Includes minimal, moderately advanced, advanced, healed and probably healed cases.

TABLE 4
Analysis by occupation and by race

OCCUPATION	PUERTO RICAN	HAWAI- IAN	CAUCA- SIAN	JAPA- NESE	CHI- NESE	FILI- PINO	KOREAN	PART- HAWAI- IAN	TOTAL
Poi maker, cook.....	13	11	79	732	166	114	7	48	1,170
Dishwasher.....	0	4	11	190	31	96	3	5	340
Cashier and bookkeeper.....	1	0	8	69	37	4	1	6	126
Waiter.....	26	30	348	1,206	312	198	42	205	2,367
Salesgirl, kitchen helper.....	35	55	268	2,415	501	212	47	172	3,705
Manager, inspector, owner, supervisor.....	4	14	215	908	380	43	23	55	1,642
Candy.....	0	0	1	9	4	5	0	1	20
Butcher.....	0	2	18	95	66	13	0	6	200
Fisherman.....	0	4	2	1	1	6	0	0	14
Dairy.....	4	1	106	143	7	38	0	7	306
Peddler.....	2	0	0	73	16	1	0	2	94
Cowboy.....	0	2	0	0	0	0	0	1	3
Bouncer.....	0	0	3	0	0	0	0	0	3
Nurse.....	0	0	1	0	0	0	0	0	1
Janitor and ice maker.....	0	0	0	6	0	0	3	0	9
Total.....	85	123	1,060	5,847	1,521	730	126	508	10,000

TABLE 5
Analysis by occupation and by diagnosis

OCCUPATION	MIN.	MOD.	ADV.	HEALED, PARTLY HEALED, CALCIF. PRIMARY	SUSP.	DOUBT.	NEG.	HEART	UNDIAG.	CERV. RIB AND OTHERS	TOTAL
Poi maker, cook.....	6	5	0	27	23	4	1,025	18	57	0	1,170
Dishwasher.....	0	3	0	12	14	0	283	6	20	2	340
Cashier and book- keeper.....	0	0	0	6	4	0	110	1	5	0	126
Waiter.....	12	4	1	40	35	7	2,187	10	64	7	2,367
Salesgirl, kitchen helper.....	7	4	1	81	73	13	3,356	35	121	14	3,705
Manager, inspector, owner, supervisor..	13	15	1	48	52	13	1,378	40	79	3	1,642
Candy.....	0	0	0	0	1	0	19	0	0	0	20
Butcher.....	3	0	0	4	8	2	172	0	11	0	200
Fisherman.....	0	0	0	0	0	0	12	2	0	0	14
Dairy.....	1	0	0	7	3	2	290	3	0	0	306
Peddler.....	0	2	0	8	2	0	80	0	2	0	94
Cowboy.....	0	0	0	1	1	0	1	0	0	0	3
Bouncer.....	0	0	0	0	0	0	3	0	0	0	3
Nurse.....	0	0	0	0	0	0	1	0	0	0	1
Janitor and ice maker.	1	0	1	0	2	1	3	1	0	0	9
Total.....	43	33	4	234	223	42	8,920	116	359	26	10,000

acteristic lesions of tuberculosis in the various stages. Eighty persons, or 0.8 per cent of them, had active tuberculosis and the great majority of these cases were discovered in the minimal or moderately advanced stages. This fact alone demonstrates the value of the mass economical X-ray examination as a means of discovering tuberculosis that is not far advanced. In all, 537 persons, or 5.79 per cent, had suspicious or characteristic lesions of tuberculosis necessitating further follow-up by X-ray studies and other epidemiological procedures.

In table 3 a comparison of the readings of 381 4" x 5" fluorograms against the same number of 14" x 17" films is made.

Table 4 describes the types of food handlers examined and the number in the various racial groups represented in the City and County of Honolulu.

Table 6 shows more cases of tuberculosis occurred among the male than female food handlers, the most significant numbers being in the group with active tuberculosis. This may be due to the fact that the males are required to seek work for the home.

TABLE 6
Analysis by sex and by diagnosis

	MIN.	MOD.	ADV.	HEALED, PARTLY HEALED, CALCIF. PRIMARY	SUSP.	DOUBT.	NEG.	HEART	UNDIAG.	CERV. RIS AND OTHERS	TOTAL
Male.....	30	28	4	117	146	28	4,326	78	195	13	4,965
Female.....	13	5	0	117	77	14	4,594	38	164	13	5,035
Total.....	43	33	4	234	223	42	8,920	116	359	26	10,000

SUMMARY AND CONCLUSIONS

The use of the 4" x 5" fluorogram has proved to be of considerable value in mass tuberculosis survey work. The films are inexpensive, accurate, easy to read and require a small amount of space for filing. In the survey in the City and County of Honolulu little or no complaint was made by the food handlers because of this requirement for employment. The majority of them appreciated this service, and they were interested in learning the condition of their chests. The survey helped make the food handlers and the community tuberculosis and X-ray conscious. Making an X-ray of the chest compulsory by regulation for such a group as large as the food handlers is one of the effective means of getting a uniform survey completed.

The number of minimal and early cases discovered in the survey demonstrates the value of this method of finding tuberculosis.

SUMARIO Y CONCLUSIONES

El empleo del roentgenograma de 10 x 12.5 cm ha resultado ser de considerable valor en las encuestas de la tuberculosis. Las películas son poco costosas, exac-

tas, fáciles de leer, y no ocupa mucho espacio al archivarlas. En una encuesta en la ciudad y condado de Honolulu, los manipuladores de alimentos protestaron muy poco o nada al imponerse este requisito para empleo. La mayoría apreció el servicio y mostró interés en conocer el estado torácico. El censo ayudó a hacer comprender a los manipuladores de alimentos y a la colectividad en general la importancia de la tuberculosis y de los rayos X. Un reglamento que haga obligatoria la radiografía torácica para un grupo tan numeroso como son los manipuladores de alimentos, representa uno de los métodos eficaces de obtener una encuesta uniforme.

El número de casos mínimos e incipientes descubiertos en la encuesta, demuestra el valor de este método para descubrir la tuberculosis.

ENZYMES AS FACTORS IN RESISTANCE TO TUBERCULOSIS¹

V. Catheptic Enzymes

BRUNO GERSTL,² ROBERT TENNANT AND OSCAR PELZMAN

The relation of proteolytic enzymes to the pathology of tuberculosis has been studied by several authors (1). Weiss, in a recent publication (2), called attention to possible effects of tuberculous infection on the activity of intracellular proteolytic enzymes. Cathepsins³ obtained from parenchymatous organs of rabbits with caseating tuberculous lesions showed reduced activity, while similar enzyme preparations from animals inoculated with a nonvirulent strain showed no such difference in their activity. Weiss (3) also showed that benzoyl-L-arginineamide as substrate for testing catheptic activity changed the results.

Another aspect of these enzymologic investigations includes the possible effect of intracellular enzymes upon components of the tubercle bacillus itself. This is suggested in one study (4), while others (5, 6, 7) report that tuberculo-protein could not be recovered from the urine after intravenous injection into tuberculous rabbits and guinea pigs as is possible with normal animals.

Studies carried out in this laboratory indicated that the resistance of various animal species to tuberculosis finds its corollary in the ability of their tissue enzymes to split tubercle phosphatide *in vitro* (8) and that immunization increases enzymatic activity (9). It was considered desirable, therefore, to study the effect of purified liver cathepsin on tuberculo-protein *in vitro*.

METHODS

Enzyme preparation: Extracts were prepared from liver by a procedure that followed that of Maver (10). The animal was exsanguinated; the liver removed, weighed and ground immediately in an ice-cooled Waring blender. The organs of at least 4 to 6 animals were pooled (9). The resulting mash was mixed with ten times its amount of 1.2 M solution of potassium chloride and stirred for an hour at 4°C. After adjustment to pH 7, the suspension was filtered through gauze and centrifuged. Then ammonium sulfate was added to 40 per cent saturation while stirring. The pH was adjusted to 5.9 with glacial acetic acid and the resulting precipitate separated and washed three times with half saturated ammonium sulfate. The residue was dialyzed against running tap water, washed with acidulated water and transferred into an 0.1 M citrate buffer, pH 5. One hundred mg. cystein hydrochloride were added for every 100 cc. of suspension and the mixture was incubated at 37°C. for seven to eight hours. The residue recovered by filtration on a Buchner funnel was dialyzed against distilled water at a temperature of 4°C.

¹ From the Laboratories of the Department of Pathology, Yale University School of Medicine. These studies have been aided by funds provided by the Research Committee of the National Tuberculosis Association, and are a part of a plan of coöperative research sponsored by the Research Committee.

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³ Cathepsin, according to Anson (J. Gen. Physiol., 1940, 23, 695), is an endocellular proteolytic enzyme presumably concerned in the processes of cellular growth, repair and inflammation.

Finally the residue was frozen and dried by lyophilization (11). The resulting powder formed a fine and stable suspension in water or in 0.1 M citrate buffer. The protein-nitrogen content of the powder, determined by the usual micro-Kjeldahl method, was corrected for the nonprotein nitrogen present.

Enzyme preparations were made from livers of normal, bovine infected and immunized rabbits, and from livers of normal guinea pigs and mice. Rabbits designated as "bovine infected" had been inoculated intravenously with 0.01 mg. tubercle bacilli strain 4717 (A.T.C.C.) per kg. and were sacrificed six weeks later. By that time the lungs were studded with caseating lesions but the livers were intact even on microscopic examination.

Immunization of rabbits as carried out in these experiments has been described elsewhere (9). Their organs were free of lesions save for a few microscopic tubercles in the spleen.

Substrates: A 2.5 per cent hemoglobin solution freshly prepared according to Anson (12) from homologous animal blood was used to test cathepsin activity.

The tuberculoprotein used as substrate was obtained through the courtesy of Doctor Lurie. It was prepared as follows: bovine, Ravenel, tubercle bacilli were grown on glycerine broth for about six weeks. The culture was filtered through Chinese silk. Enough 5 per cent carbolic acid was added to make an 0.5 per cent solution. This was filtered through a Seitz filter. Then it was ultra-filtered through an alundum cup covered with a 14 per cent nitrocellulose membrane until free of chlorides. The material retained by the cup was dried *in vacuo* over calcium chloride and gave a positive tuberculin reaction in tuberculous guinea pigs in quantities as low as 0.001 mg.

Reaction mixtures for testing cathepsin activity: Enzyme reaction mixtures were set up as follows: the enzyme powder was suspended in 10 ml. water. Then 9.6 ml. of the hemoglobin solution, 2.4 ml. acetate mixture (12) and 12 ml. M/10 citrate buffer, pH 4.3 were added and finally freshly prepared cystein hydrochloride solution in the desired concentration. The volume was then made up to 36 ml. with water.

Duplicate aliquots of 3 ml. and each containing an amount of cathepsin equivalent to 0.138 mg. protein nitrogen were taken at suitable intervals. They were precipitated with 5 ml. of 0.33 N-trichloroacetic acid. Enzyme activity was estimated with an Evelyn photoelectric colorimeter (13) by determining the amount of tyrosin present in the aliquots.

Control reaction mixtures incubated without substrate did not contain any split-products that reacted with the Folin-Ciocalteu reagent, nor did this extract exhibit any butyrase activity. Monophosphoesterase activity, however, could be demonstrated.

Reaction mixtures for testing the effect of liver cathepsins on tubercle protein: The components of the reaction mixtures were in the same proportions as in those described before, except that tubercle protein was added as substrate instead of hemoglobin. Its final concentration was 10 mg. per ml. reaction mixture. Cleavage of tubercle protein was estimated by determining the total nonprotein nitrogen in the aliquots. By employing the method of Rappaport (14), 20 to 100 gamma of nitrogen could be estimated with an accuracy of ± 4 per cent. The amino acid concentration was also estimated on duplicate aliquots (15).

RESULTS

A. Cathepsin activity: The cathepsin activities of normal mouse, rabbit and guinea pig are reported in tables 1, 2 and 3. The addition of l-cystein effected a marked activation with a maximum obtained by a molar concentration of 1/2500 in the case of the rabbit and guinea pig liver. With the mouse liver,

however, the three different concentrations of cystein accomplished identical activation.

TABLE 1
Catheptic activity of mouse liver

DATE OF EXPERIMENT	ACTIVATOR	TIME OF INCUBATION			
		15 min.	30 min.	45 min.	60 min.
		Amount of splitting in mg. of tyrosin			
12/17/43	—	.0087	.0247	.0448	.0572
12/24/43	—	.0154	.0263	.0428	.0626
1/28/44	—	.0136	.0231	.0392	.0685
1/28/44	1-cystein, 1/1000M	.0000	.0980	.1100	.1120
12/17/43	1-cystein, 1/2500M	.0150	.0327	.0609	.0799
1/28/44		.0350	.1360	.1460	.1000
12/17/43	1-cystein, 1/10,000M	.0089	.0281	.0485	.0560
1/28/44		.0518	.0709	.0719	.1148

TABLE 2
Catheptic activity of normal rabbit liver

DATE OF EXPERIMENT	ACTIVATOR	TIME OF INCUBATION			
		16 min.	30 min.	45 min.	60 min.
		Amount of splitting in mg. tyrosin			
5/17/43	—	.0271	.0693	—	.1166
5/18/43	—	.0294	.0550	.1060	.1200
11/11/43	—	.0322	.0344	.0543	.0760
11/15/43	—	.0384	.0496	.0552	.0815
1/20/44		.0157	.0427	.0459	.0523
1/20/44	1-cystein 1/1000M	.0060	.0265	.0280	.0470
11/15/43	1-cystein 1/2500M	.0419	.0677	.0915	.1283
1/20/44	1-cystein 1/2500M	.0217	.0344	.0541	.0663
11/15/43	1-cystein 1/10,000M	.0438	.0560	.0780	.0981
1/20/44	1-cystein 1/10,000M	.0198	.0234	.0442	.0292

Considerable variation in activity was found with different enzyme preparations. If averages are taken (table 4), the activity of the fully activated guinea pig liver was slightly higher than that of mouse or rabbit under comparable conditions.

A second group of experiments concerned the cathepsin activity of liver

from immunized and bovine infected rabbits (chart 1). Extracts from immunized animals showed two or more times as much activity as the normal ones. Those from rabbits inoculated with bovine tubercle bacilli had the same activity as the normal ones with the exception that cystein had no activating effect.

TABLE 3
Catheptic activity of guinea pig liver

DATE OF EXPERIMENT	ACTIVATOR	TIME OF INCUBATION			
		15 min.	30 min.	45 min.	60 min.
		<i>Amount of splitting in mg. tyrosin</i>			
4/20/44	—	.0250	.0565	.0836	.1066
4/25/44	—	.0276	.0512	.0631	.0710
4/20/44	1-cystein 1/1000	.0102	.0940	.0982	.1150
4/25/44	1-cystein 1/1000	.0250	.0620	.1060	.1120
4/20/44	1-cystein 1/2500	.0325	.0722	.1213	.1370
4/25/44	1-cystein 1/2500	.0406	.0725	.0904	.1140
4/20/44	1-cystein 1/10000	.0286	.0556	.0781	.0912
4/25/44	1-cystein 1/10000	.0335	.0604	.0826	.1003

TABLE 4
Activity of liver cathepsins (average values)

	ACTIVATOR	TIME OF INCUBATION			
		15 min.	30 min.	45 min.	60 min.
		<i>Amount of splitting in mg. tyrosin</i>			
Mouse.....	—	.0126	.0247	.0423	.0628
Rabbit.....	—	.0286	.0502	.0654	.0893
Guinea pig.....	—	.0263	.0539	.0733	.0888
Mouse.....	1-cystein 1/2500	.0250	.0843	.1034	.0900
Rabbit.....	1/2500	.0318	.0510	.0728	.0973
Guinea pig.....	1/2500	.0365	.0724	.1058	.1255

Weiss (3b) also reported that tuberculo-protein inhibits proteinases. This was tested by employing gelatine as substrate with tuberculin added as possible inhibitor. Cleavage was determined by estimating the increase of nonprotein nitrogen in the reaction mixtures. There was no difference between the reaction mixtures containing tuberculin and those without.

B. *Effect of liver cathepsins on tuberculo-protein:* Liver cathepsin preparations

obtained from normal as well as from immunized rabbits were incubated with tuberculo-protein under addition of 1/10M citrate buffer, pH 4.0. A second group of reaction mixtures contained cystein hydrochloride in 1/2500M concentration as activator. At 0, three- and six-hour intervals, aliquots were taken and precipitated with trichloroacetic acid.

There was no indication of cleavage of tuberculo-protein by either method.

The possibility that some factor contained in less well purified preparations might bring about the cleavage of tuberculo-protein was considered. Mashed rabbit liver was extracted with chilled acetone and ether, and the resulting powder employed as source of enzymes. But no splitting of tuberculo-protein was observed.

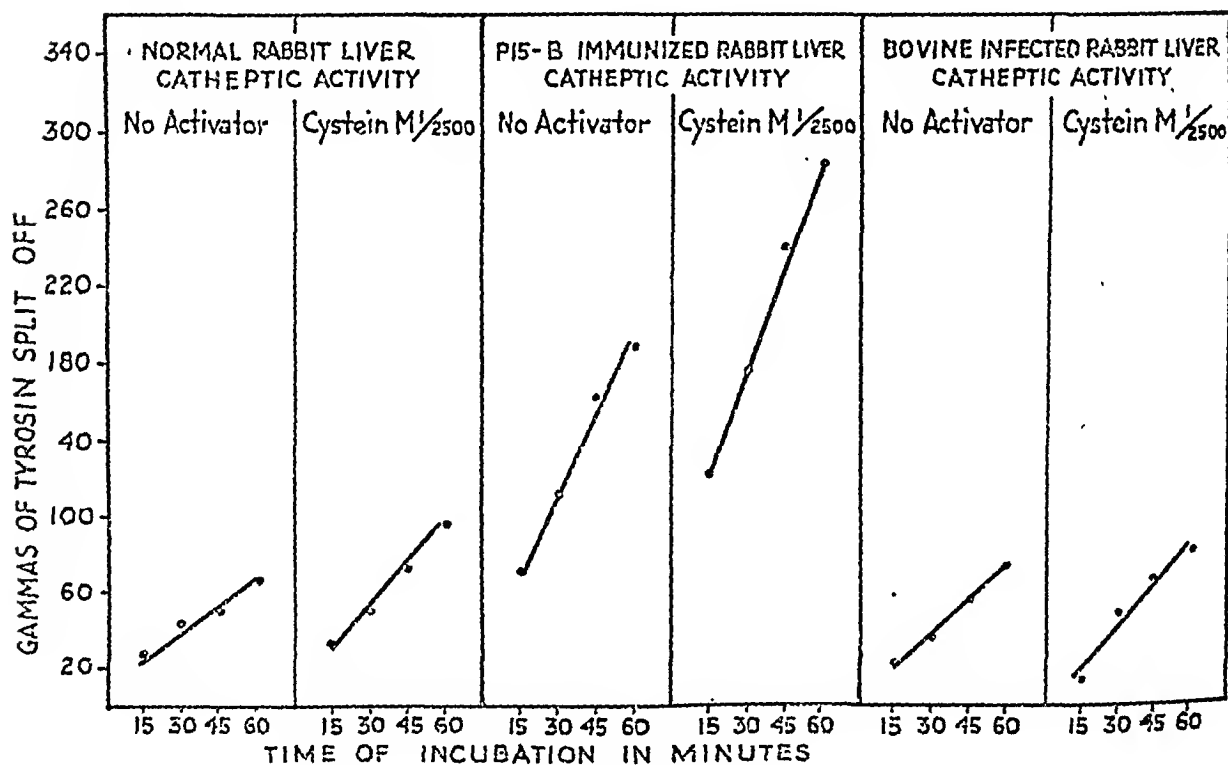


CHART 1

COMMENT

The studies of Weiss (l.c.) as well as the investigations reported here indicate that the endocellular cathepsins of the liver undergo marked alteration when an animal is inoculated with tubercle bacilli. Weiss observed that the concentration of cathepsins was reduced when rabbits were reinfected with virulent bovine tubercle bacilli, while reinfection with nonvirulent cultures failed to produce changes. In subsequent experiments Weiss (3) found that cathepsins obtained from rabbits inoculated with a nonvirulent culture also showed reduced activity. He sought to explain this phenomenon by assuming that tubercle phosphatide liberated from disintegrated tubercle bacilli inhibited cathepsin activity. In

these experiments, there was no reduction of cathepsin activity with extracts from livers of tuberculous rabbits.

The inhibitory effect of tubercle phosphatide upon another enzyme system had been observed earlier in this laboratory. This may have been due to factors other than true inhibition like the adsorbing effect of colloidal suspensions such as that of tubercle phosphatide, since lecithin and cephalin suspensions are known to inhibit dipeptidase (16). Later, it was shown (17) that fatty acids similar to those of the tubercle bacillus are the inhibiting agents. In the case of liver enzymes, however, and particularly those of the rabbit, it is doubtful that these factors come into play because the anatomical findings do not indicate the presence of large numbers of bacilli in the liver.

The catheptic activity in immunized rabbits, on the other hand, is extraordinarily high and significantly greater than individual variation of the different lots. This raises the question whether the increase of enzymatic activity due to sensitization with avirulent bacilli is part of the humoral mechanism of immunization. It is the opinion of many authors that necrosis takes place when great concentrations of antigen meet antibodies in the tissues. This is followed quickly by an acute inflammatory reaction (Forbus (18)). The increase of cathepsins would provide faster removal of the necrotic tissue.

The results of the second group of experiments indicate that tubercle protein is not attacked by tissue cathepsins, whether they are derived from normal or immunized rabbits. This would explain the appearance of a protein-like, immunologically active substance in the urine after injection of tubercle protein (l. c.). The observation that this substance does not occur in the urine when tuberculous guinea pigs are used is probably due to retention of tubercle protein in the tissue and not to its cleavage.

SUMMARY

1. Cathepsin preparations of livers of 3 species (mouse, rabbit and guinea pig) when fully activated showed little difference in activity.

2. The catheptic activity of enzyme preparations obtained from livers of immunized rabbits was twice or more of that of normal rabbits; that of livers from rabbits inoculated with virulent bovine tubercle bacilli was of the same magnitude as that of extracts from normal rabbits.

3. Tuberculoprotein did not inhibit catheptic activity under the conditions of these experiments.

4. Liver cathepsin preparations obtained from normal as well as immunized rabbits did not effect any cleavage of tuberculoprotein.

SUMARIO

1. Las preparaciones de catepsina hepática de tres especies animales (ratón, conejo y cobayo) revelaron poca diferencia en su actividad al ser plenamente activadas.

2. La actividad catéptica de las preparaciones enzimáticas obtenidas de los hígados de los conejos inmunizados, fué el doble o más que la de los conejos

normales; y la de los hígados de los conejos inoculados con bacilos tuberculosos bovinos virulentos, reveló la misma magnitud que la de los extractos de los conejos normales.

3. La tuberculoproteína no inhibió la actividad catéptica en las condiciones de estos experimentos.

4. Las preparaciones de catepsina hepática obtenidas de conejos normales así como inmunizados no produjeron disociación alguna de la tuberculoproteína.

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THE SPECIFIC CYTOTOXIC ACTION OF TUBERCULIN

The Reaction of Tissues from Animals Sensitized with Heat-Killed Tubercle Bacilli

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Since Rich and Lewis (1) demonstrated the specific cytotoxic action of tuberculin in tissue cultures, other workers also have noted that cultures of certain tissues of tuberculous animals are quite regularly damaged by concentrations of tuberculin that do not affect the growth of tissue obtained from normal animals (2 to 5). We also have reported similar studies (6) and have noted a significant specific cytotoxic response in almost all of the tuberculous animals that we have studied. In order to avoid the use of infectious material in certain phases of our work, it seemed desirable to investigate the relative cytotoxic response to tuberculin of tissues from rabbits made hypersensitive to tuberculin by the injection of heat-killed tubercle bacilli suspended in petrolatum. It was also of some theoretical interest to know whether or not a cellular sensitivity to tuberculin also would develop in animals rendered skin-sensitive to tuberculin by heat-killed tubercle bacilli.

In 1909 Römer (7) reported that the injection of heat-killed tubercle bacilli could establish hypersensitiveness to tuberculin in a certain number of animals. This was confirmed by Baldwin (8), Bessau (9) and other investigators. The work of Zinsser and Petroff (10) and Petroff and Stewart (11) indicated that all of the allergic phenomena found in tuberculous animals were manifest in animals sensitized with heat-killed organisms. Freund and Opie (12) studied the effects of various methods of injecting rabbits with heat-killed tubercle bacilli. They found that there was no relation between the degree of sensitization produced, the amount of antibody and the amount of resistance to infection with *Mycobacterium tuberculosis*. Many reports have appeared on the use of heat-killed tubercle bacilli for developing hypersensitivity and immunity; nevertheless, results with this method of producing hypersensitivity without infection were not always satisfactory.

Vallée (13) in 1924 stated that cattle inoculated with dead tubercle bacilli suspended in paraffin oil retained the vaccine at the site of injection for at least two years. Coulaud (14) developed hypersensitivity in rabbits by the injection of melted paraffin and killed tubercle bacilli. Saenz (15) reported the development of profound and lasting skin sensitivity to tuberculin in guinea pigs inoculated with heat-killed tubercle bacilli suspended in paraffin oil. Saenz (16) observed that the skin reaction to tuberculin in guinea pigs sensitized in this manner was characterized by the presence of edema and the occurrence of a large hemorrhagic region which later became necrotic. The hemorrhagic reaction occurred more often in guinea pigs which were inoculated in the testes or lungs than in those inoculated subcutaneously. Freund, Casals and Hosmer

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(17) reported that paraffin oil augmented sensitization by dead tubercle bacilli and the formation of complement fixing antibodies in both guinea pigs and rabbits. Casals and Freund (18) were able to develop complement fixing antibodies and skin sensitivity to tuberculin in monkeys by inoculating them with dead tubercle bacilli in paraffin oil. Freund and Gottschall (19) found it satisfactory to use guinea pigs sensitized by killed tubercle bacilli in liquid petrolatum for the standardization of tuberculin.

METHODS

Animals: Adult male rabbits were used exclusively. Two strains of *Mycobacterium tuberculosis* of the human type were used to induce sensitivity, strain H439 (Feldman), which has been described previously, grown on egg-yolk-glycerin-agar culture medium for six weeks, and a two weeks' old culture of *Mycobacterium tuberculosis* H37RV grown on Proskauer-Beck synthetic liquid medium. In each instance the bacillary growth was removed and placed in a tube in a small amount of sterile physiological salt solution and heated in a water bath at 80°C. for one hour. A portion of each suspension of heat-killed organisms was injected subcutaneously into 2 guinea pigs to determine sterility. No evidence of tuberculosis was found in the inoculated guinea pigs when they were killed and examined sixty days after inoculation.

The heat-killed tubercle bacilli were removed from suspension, partially dried, weighed and ground in a mortar under sterile conditions. A small amount of paraffin oil was added to petrolatum jelly to bring the melting point to 50°C. This mixture was sterilized and mixed with the dead tubercle bacilli so that each cubic centimeter of petrolatum contained 5 mg. of bacilli. Rabbits were etherized, and 1 cc. of the mixture of killed tubercle bacilli in petrolatum was injected into each testis. Intracutaneous tuberculin tests were performed at various times after two and a half weeks from the time of inoculation. Tissue culture studies were made after the development of skin sensitivity and within two weeks of the demonstration of a positive reaction (that is, an area of induration and erythema 0.5 cm. or more in diameter forty-eight hours after the intracutaneous injection of 1 mg. OT). The period of sensitization was between eight and thirty-three weeks. Data relating to the animals used in this series of experiments are presented in table 1.

In addition, 2 rabbits were given an injection of 1 cc. of petrolatum alone into each testis. Explants of spleen from one of these animals were tested in tissue culture for sensitivity to tuberculin. Two rabbits were given an injection, into each testis, of 1 cc. of petrolatum containing 2 mg. of Old Tuberculin and 2 rabbits were inoculated in the same way with petrolatum containing 0.01 mg. per cc. of PPD manufactured for intracutaneous testing.

Precipitin tests: Blood was drawn from the rabbits at various times during the period of sensitization for determining the presence of precipitins for Old Tuberculin. The ring precipitation test was used. Approximately 0.2 cc. of undiluted serum was placed in several small tubes having an inside diameter of 4 mm. and equal amounts of different dilutions of Old Tuberculin in physiological salt solution were carefully layered above the serum. Preservative-free mammalian

tuberculin of the human types was used in the precipitin tests.³ Observations were made after two hours of incubation at 37°C. and the development of precipitate at the interface between the two liquids was recorded as a positive result. As a control, precipitin tests were also done with sera taken from 10 normal rabbits and 6 rabbits infected with a human strain of *Mycobacterium tuberculosis* (Feldman, 439).

Tissue culture methods: The quantitative tissue culture method used in the present study has been described in a previous publication (6). Splenic tissue was removed from a normal rabbit and from a rabbit inoculated with the test substance. Suitable explants were prepared and cultured in D5 Carrel flasks in medium containing tuberculin as well as in medium that did not contain tuberculin. Two samples of preservative-free mammalian tuberculin of Old Tuberculin strength were used.⁴ Sample A was employed in a final concentration of 1:500 and sample B, which was approximately twice as strong, was used

TABLE 1

Sensitization of rabbits to tuberculin by the intratesticular injection of heat-killed tubercle bacilli in petrolatum

RABBIT	STRAIN OF MYCOBACTERIUM TUBERCULOSIS USED TO SENSITIZE	DURATION OF SENSITIZATION	PRECIPITIN TITRE, DILUTION OF OT
		<i>weeks</i>	
K 756	H439	16½	1:1,800
K 757	H439	18	1:1,800
L 21	H439	33	1:2,000
72	H37 R Variant	8	1:10,000
79	H37 R Variant	18	1:10,000

in a concentration of 1:1,000. Tissue culture medium was prepared with plasma and serum obtained from the blood of a normal rabbit as previously described. In addition, in experiments with tissue of rabbits sensitized with heat-killed tubercle bacilli, a duplicate experiment was done using medium prepared with plasma and serum of a sensitized rabbit.

The extent of migration of large wandering cells from the spleen was determined in all cultures with the use of an ocular micrometer on the fourth day of incubation at 37°C. The average radius of the zone of migration in test cultures was compared with that observed in control cultures in the presence and absence of tuberculin. The results were expressed in terms of a comparative cytotoxic index according to the formula:

Comparative cytotoxic index

$$= \frac{\text{Average migration (N)}}{\text{Average migration (N + OT)}} \times \frac{\text{Average migration (S + OT)}}{\text{Average migration (S)}}$$

³ Obtained through the courtesy of the Bureau of Animal Industry of the United States Department of Agriculture.

⁴ Obtained through the courtesy of the Bureau of Animal Industry of the United States Department of Agriculture.

in which N = cells from normal tissue and S = cells from tuberculin-sensitive tissue. A numerical value less than 1 is an indication that tuberculin has a specific damaging effect on tissue of sensitized animals.

Cultures were incubated for six days, and the extent of growth of fibroblasts was observed.

RESULTS

Intracutaneous tuberculin tests: Positive skin reactions to Old Tuberculin were observed during the third and fourth week after the injection of killed tubercle bacilli in petrolatum. Immediate reactions to the intracutaneous injection of tuberculin were not observed, but reactions developed between twenty-four and forty-eight hours and reached their maximal intensity at about forty-eight hours. The reactions observed differed somewhat from those seen in rabbits with experimental tuberculosis. In rabbits sensitized with killed tubercle bacilli the skin reaction was larger and thicker and the edema was more pronounced than in infected animals. The skin reactions observed in the present study were pale with less diffuse redness than is usually present in a typical tuberculin reaction, and petechiae were usually present. Necrotic reactions were not observed.

Rabbits that received injections of petrolatum alone did not show a reaction to the intracutaneous tuberculin test. Both rabbits inoculated with petrolatum containing Old Tuberculin and tested six weeks after injection showed the following kind of reaction. Thirty minutes after the intracutaneous injection of tuberculin a pale wheal measuring 20 mm. in diameter appeared at the site of injection. Four hours after injection the wheal was approximately 30 mm. in diameter; then it decreased in size until a small patch of edema 5 mm. in diameter was present twenty hours after injection. Slight redness of the edematous patch was noted at this time. No reaction was visible forty-eight hours after injection.

The response of the 2 rabbits inoculated with petrolatum and PPD to the intracutaneous tuberculin test was also distinctive. An immediate reaction was not present in either instance, but a pale patch of edema measuring approximately 10 mm. in diameter appeared about eight hours after injection. The swelling disappeared gradually and the skin appeared normal at forty-eight hours.

Precipitin reactions: In all of the rabbits sensitized to tuberculin by the injection of killed tubercle bacilli in petrolatum, precipitins for tuberculin developed. Although animals were not tested at regular frequent intervals it was observed that antibodies appeared at about the same time skin sensitivity occurred and were present until the end of the period of observation. The titres of sera obtained at the time tissue culture studies were made are recorded in table 1. Sera from 10 normal rabbits and 6 rabbits experimentally infected with a strain of *Mycobacterium tuberculosis* of the human type (Feldman H439) did not give a precipitin reaction with Old Tuberculin. The highest concentration of tuberculin used in the test was 1 to 20. Precipitins were not observed in the sera of rabbits that received injections of petrolatum alone or of petrolatum containing Old Tuberculin or PPD.

Tissue culture experiments: The microscopic appearance of cultures of splenic explants from normal rabbits and from rabbits with mild tuberculosis has been described previously (6). Cultures of explants from rabbits sensitized by the injection of killed tubercle bacilli in petrolatum qualitatively resembled those of explants from rabbits with mild tuberculosis and showed the same morphological changes in the presence of tuberculin. The extent of migration of wandering cells in explants from rabbits sensitized with killed tubercle bacilli was not as great as in explants from tuberculous animals. In other words, a stimulated activity of the large wandering cells was not observed. Cultures of the spleen of rabbits that received injections of petrolatum and petrolatum containing Old Tuberculin or PPD resembled cultures of the normal spleen.

TABLE 2

Comparative cytotoxic effect of tuberculin on migration of cells from explants of spleen of normal rabbits and rabbits inoculated with heat-killed tubercle bacilli in petrolatum

RABBIT	TUBERCULIN USED IN CYTOTOXIC TESTS	COMPARATIVE CYTOTOXIC INDEX	
		Medium prepared with blood of normal rabbit	Medium prepared with blood of sensitized rabbit
K 756	A	0.74	0.56
K 757	A	0.98	0.90
L 21	A	0.43	0.50
72	B	0.60	0.55
79	B	0.25	0.31

TABLE 3

Comparative cytotoxic effect of Old Tuberculin, sample B, on migration of cells from explants of spleen of normal rabbits and rabbits that received injections of petrolatum or petrolatum containing OT or PPD

RABBIT	PREPARATORY INJECTION	COMPARATIVE CYTOTOXIC INDEX
83	2 cc. petrolatum	1.01
49	2 cc. petrolatum + 4 mg. OT	1.05
86	2 cc. petrolatum + 0.02 mg. PPD	0.89
82	2 cc. petrolatum + 0.02 mg. PPD	1.01

Of the 5 rabbits sensitized with killed tubercle bacilli, the tissues of 4 showed a specific cytotoxic response to tuberculin, whereas in one instance (rabbit K 757) a specific cytotoxic effect was not observed. The results of quantitative determinations of the relative degree of migration of macrophages in control and test cultures are presented in table 2. In general the relative inhibition of sensitive cells by tuberculin was about the same in medium made with serum and plasma from the normal or the sensitized rabbit. The growth of fibroblasts from tuberculin-sensitive explants was also decreased in medium containing tuberculin. In a small number of tests a specific cytotoxic response to tuberculin was not observed in animals that previously received injections of petrolatum alone or petrolatum containing Old Tuberculin or PPD (table 3).

COMMENT

Although cellular sensitivity to tuberculin resulted in most instances from the injection of heat-killed tubercle bacilli in petrolatum, the results were not as uniform as those obtained in a previous study with tuberculous rabbits. The same samples of tuberculin were used in cytotoxic tests in both studies and experiments reported in this paper and in the previous paper (6) were done at about the same time. The reason for the failure of one sensitized rabbit to show a specific cytotoxic response is not known. The reactions to the intracutaneous tuberculin test in this animal were as marked as in other rabbits in the same group, and precipitins for Old Tuberculin were present in the blood. This animal appeared to be in good condition at the time it was used for tissue culture studies.

The presence of antibodies in the serum of sensitized rabbits did not affect the degree of cellular sensitivity to tuberculin when these antibodies were present in the culture medium. It is obvious that antibodies could not be entirely removed from explants of sensitized rabbits by washing with Tyrode's solution. Nevertheless, if the antiserum present had any effect on the cellular sensitivity to tuberculin, it seems likely that the quantitative methods used would have detected a difference in the effect of the same amount of tuberculin in the presence of a small or large amount of antiserum.

Laidlaw and Dudley (20) showed that a complex carbohydrate fraction in tuberculin is responsible for the development of a precipitate with serum from animals hyperimmunized with dead tubercle bacilli. They also found that polysaccharide was not capable of causing the formation of antibodies and they expressed the view that a protein-polysaccharide complex was necessary for the formation of antibodies. Their observations have been substantiated by the work of other investigators. The failure of immune serum to modify the specific cytotoxic reaction to tuberculin is in agreement with the failure of antibody to influence the local or general reaction to tuberculin in tuberculous animals. Although a combination of polysaccharide with some other molecule, perhaps protein, is necessary for the production of precipitins, this antibody apparently does not react with the protein derivative responsible for eliciting the tuberculin reaction, either *in vivo* or *in vitro*. The complex necessary for the formation of antibodies is evidently not present in Old Tuberculin or PPD, and Masucci, McAlpine, and Glenn (21) found that it was not present in the culture filtrate from which bacilli had been removed.

The results of experiments with the injection of Old Tuberculin and PPD in petrolatum are in agreement with the results of similar attempts by other investigators to induce tuberculin sensitivity or the formation of antibodies with products of the tubercle bacillus. In this study, rabbits that received injections of Old Tuberculin in petrolatum showed an immediate wheal formation after the intracutaneous injection of tuberculin, which suggested an anaphylactic type of sensitivity. The small wheal which appeared about eight hours after the intracutaneous injection of tuberculin into rabbits that previously received injections of PPD in petrolatum may have indicated a low degree of the same kind of sensi-

tivity, but further studies were not carried out to determine the nature of the reaction.

SUMMARY AND CONCLUSIONS

The intratesticular injection of heat-killed tubercle bacilli suspended in petrolatum into rabbits resulted in the development of a specific cytotoxic response in 4 of 5 instances. Although the degree of cellular sensitivity to tuberculin was marked in some instances, a good deal of variation existed in the results obtained with different rabbits. For this reason, explants of spleens from rabbits sensitized with heat-killed tubercle bacilli are not as satisfactory for tissue culture studies as explants from tuberculous rabbits.

In all rabbits that received injections of killed tubercle bacilli in petrolatum, a well-marked skin sensitivity and precipitating antibodies to Old Tuberculin developed. The presence of precipitins for Old Tuberculin in the tissue culture medium did not alter the specific cytotoxic activity of tuberculin.

SUMARIO Y CONCLUSIONES

En 4 de 5 casos la inyección intratesticular en el conejo, de bacilos tuberculosis muertos por calor y suspendidos en petrolato produjo una respuesta citotóxica específica. Aunque la intensidad de la sensibilidad celular a la tuberculina fué prolongada en algunos casos, observóse mucha variación en los resultados obtenidos en distintos conejos, por cuya razón los explantes de bazos procedentes de conejos sensibilizados con bacilos tuberculosos muertos al calor no resultan tan satisfactorios para los estudios de cultivos histológicos como los procedentes de conejos tuberculosos.

En todos los conejos que recibieron inyecciones de bacilos tuberculosos muertos en petrolato presentáronse hipersensibilidad cutánea y anticuerpos precipitantes a la tuberculina antigua. La presencia de precipitinas para la tuberculina antigua en el medio de cultivo de tejido no alteró la actividad citotóxica específica de la tuberculina.

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CHEMOTHERAPY IN EXPERIMENTAL TUBERCULOSIS^{1, 2}

Tests *in vitro* and *in vivo* with Different Types of Agents

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With the technical assistance of H. B. Moy

Chemotherapeutic trials in animal tuberculosis were made in great number immediately after the introduction of the sulfonamides into medicine. All of the common sulfonamides were found to exert at least a deterrent effect on tuberculosis in guinea pigs. Thus, Rich and Follis (1) found that the tuberculous lesions produced in guinea pigs were less extensive in animals treated with sulfanilamide. More recent results are similar, even with more potent sulfonamides, as shown by a report of Ballou and his coworkers (2). In 1942, these authors found that sulfathiazole exerted an inhibitory effect in experimental tuberculosis, but this was not sufficient to justify clinical trials.

More encouraging results have been reported with the diaminodiphenylsulfone derivative called "promin" (sodium p,p'-diaminodiphenylsulfone-N,N'-dix-trosulfanate). Feldman and his coworkers (3), as well as other investigators, have shown that the administration of promin notably limits the development of tuberculosis in guinea pigs, as compared to that in untreated controls. The best results were obtained when the inocula of tubercle bacilli were very small, and when large guinea pigs were used. Later Feldman, Hinshaw and Moses (4) reported that "diasone" (disodium formaldehyde sulfoxalate diaminodiphenylsulfone) was superior to promin in being slightly less toxic, and still later (5) that "promizole" (4,2'-diaminophenyl-5'-thiazole sulfone) was superior to the preceding drugs. Several related compounds have been shown to exert somewhat similar effects (6, 7). Reports of the clinical trial of these compounds have been notably reserved as to the estimate of their final therapeutic value (8).

Recently, many other compounds, unrelated to the sulfonamides, have also been suggested. These include cadmium sulfide (9), benzophenone (10), chlorophyl (11), 2,3,5 triiodobenzoate (12), methyl-isopropyl-phenol (13), wetting agents (14), thymol (15) and propamidine (16).

The problem of chemotherapy in tuberculosis lends itself to the testing of agents *in vitro* and *in vivo*. *In vitro*, many agents may be tested rather easily by their incorporation in a medium upon which tubercle bacilli are subsequently seeded. *In vivo*, the more difficult character of the experiment tends to restrict the number of agents that may be tried. The sensitive guinea pig may succumb to intercurrent disease or the toxicity of the compound, and a large number of

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animals are needed because of the variable response to tuberculous infection. Also, certain compounds are not available in quantities adequate for tests in animals. Perhaps most important, the final point of comparison usually must be made, not on life versus death, but on the relative degree of organ involvement in control and test animals.

Our program has been to test all available compounds first *in vitro*, and then to try in guinea pigs those agents which gave promising results *in vitro*. Substances which might be active only *in vivo* would, of course, be missed by this procedure, but it was not felt that the time and expense necessary to test all compounds in animals could be justified.

IN VITRO TESTS

For the *in vitro* studies, human tubercle bacilli of the Stanford 0-28 strain² were grown at 37°C. on a solid medium containing egg, veal infusion broth, peptone and glycerin, buffered to a reaction of pH 7.2 to 7.4. In control tubes, colonies of tubercle bacilli appeared within two weeks, and became luxuriant in four to six weeks. The agents to be tested were mixed with the medium before it was autoclaved, which limited the tests to compounds unaffected by this degree of heat. In some instances, the insolubility of the compounds lowered the concentration at the surface of the media.

Each compound was tried routinely in 5 separate tubes, in a concentration of 40 or 20 mg. per 100 cc. of medium. When inhibition of the growth of tubercle bacilli occurred, further tests were made, and the concentrations of the agent were reduced successively to 10, 5 and 2.5 mg. per 100 cc. Compounds which produced inhibition in concentrations of 10 mg. per 100 cc., or less, were called highly active; those which produced inhibition only in concentrations greater than 10 mg. per 100 cc. were called slightly active; those which failed to modify the growth as compared with the controls were called inactive.

A total of over 300 compounds, obtained from diverse sources, were tested. Some were obtained commercially, some synthesized by us and some kindly supplied by the following organizations: Shell Development Company, Emeryville, California; Monsanto Chemical Company, St. Louis; Frederick Stearns and Company, Detroit; Abbott Laboratories, North Chicago, Illinois; American Cyanamid Company, New York City; and the Western Regional Research Laboratory, U. S. Department of Agriculture, Albany, California.

The results of the *in vitro* trials are shown in the following tabulation.

Sulfonamide Derivatives

Slightly active

sulfadiazine

thiocarbonyldisulfanilamide

diasone

neosynephrene sulfathiazolate

p-diphenylaminobisazosulfanil-
amide

m-ethylphenylazosulfanilamide

² Originally obtained from Saranac Lake Sanatorium by Dr. E. W. Schultz, of the Stanford Department of Bacteriology.

*Sulfonamide Derivatives—Continued**Inactive*

sulfanilamide
 sulfathiazole
 sulfadiazine
 promin
 dichlorosulfanilamide
 cholic acid-sulfanilamide
 carbonyl disulfanilamide
 o-hydroxybenzalsulfanilamide

 roseanilinediazosulfanilamide
 urea disulfanilamide
 urea monosulfanilamide
 aminodiphenylsulfone

m-hexalbenzalsulfanilamide
 bromosulfanilamide
 sulfathiazole with "Aerosol" and
 other wetting agents
 aminopyridineazosulfanilamide
 sodium β naphthalate tribromo-
 azosulfanilamide
 8-sodium quinolate-5-azosulfa-
 nilamide
 aminodiphenylsulfoneazosulfa-
 nilamide
 benzedrinesulfanilamide
 saccharinesulfanilamide

The inactivity of promin may have been due to the fact that, under *in vitro* conditions, it was not split to diaminodiphenylsulfoné, as may occur *in vivo*. There is no doubt that the sulfonamide nucleus exerts a slight inhibitory effect on tubercle bacilli *in vitro*.

Sulfolanyls

Highly active: sulfolanylamine

Slightly active

sulfolane (butadienemonosulfone)
 dimethylsulfolane

monoethylsulfolane

Inactive

dibromosulfolane
 sulfolanylsulfanilamide
 N₃sulfolanyl-p-acetyl aminoben-
 zenesulfonamide
 acetyl N-allyl-N-sulfolanyl-
 sulfanilamide
 sulfolanol
 methylsulfolanyl ether

 normal decylsulfolanyl ether

allylsulfolanylether
 sulfolanylacetate
 sulfolanyloleate.
 sulfolanyl substituted with:
 $X-OCH = CH(CH_2)_7CO$
 3,3,5,trimethylcyclohexol sulfo-
 lanyl ether
 2,4-dimethylsulfolanesulfolanyl-
 ether
 allylsulfolanylsulfanilamide

Part of the effect of butadiene monosulfonamide (sulfolanylamine) may have been due to its alkalinity, as the neutralized compound was inactive.

Plasticizers

Inactive: Monsanto Santicizers 1H, 8, 9 and 10

This attempt to inhibit the bacillus through an effect on the moulding of its capsular substance was unsuccessful.

Heavy Metals

Highly active: sobisminol

Inactive

gold sulfauramine
 sodium bismuthate

sodium arsanilateazosulfanilamide

Sobisminol showed considerable activity, but sodium bismuthate, the active metallic compound, was inactive. A mixture of triisopropanolamine and propylene glycol, the alkaline vehicle in sobisminol, showed considerable activity. Triethanolamine, another alkaline amine, showed a high degree of inhibition, which was lost when it was neutralized.

Chaulmoogra Derivative

Highly active: ethyl chaulmoograte

Phenothiazine Derivatives

Slightly active

phenothiazine	fluorone
phenothiazone	diphenylene oxide
thionol	dihydroxymethylacridan
phenothioxin	alpha-hydroxyphenazine

Inactive

phenazine	dibenzthiophen
diphenyl	alpha-beta-phenazine
dimethylacridan	phenothiazine sulfoxide

Acridine Derivatives

Highly active

10-methyl-3-6-aminoacridine- azosulfanilamide	acridine orange CI 788
neutral acriflavine	2-ethoxy-6,9-diaminoacridine- azosulfanilamide

Slightly active

aminoantipyrinsulfanilamide
phenylacridine

Inactive

2-ethoxy-6,9-diaminoacridine- azosulfanilamide	pyridium
2-ethoxy-6,9-diaminoacridine- sulfapyridine	2 butyloxy-2,6'-diamino 5,5' azopyridine
tryptflavineazosulfanilamide	thioacridine
atabrine	methylether of thioacridine
	butylphenylacridine

Certain of the acridines, especially the first three of the list above, were more active than any other compounds tested, except ethyl chaulmoograte.

Dyes

Highly active

capri blue	azur I
methylene blue	ethyl red
azur A	acridine yellow R
azur B	janus black
azur C	

Slightly active

lauth's violet	chrome yellow
ethyl violet	nile blue sulfate
sun yellow	azo rubin
naphthylamine yellow, brown, and red	diazine green

*Dyes—Continued**Inactive*

congo red
soluble iodophthalein
crystal violet
p-rosaniline base O
malachite green oxalate
night blue
victoria blue
lyon's blue
rhodamin
acid brown
magdala red
benzopurpurin
para blue
patent blue
brilliant green
biebrich scarlet
alkali blue
thiazin brown
bordeaux R
porrier's blue
stilbene yellow
quinoline yellow
foist yellow
pyoktanin yellow
mikado yellow
yellow KM
brilliant yellow
yellow 66
amaranth
aniline blue black
alkalie green D
acid green 6

auramineazosulfanilamide
sudan I
sudan II
sudan III
sudan IV
azo blue
fat ponceau
ponceau 3R
scarlet B
scarlet G
scarlet R
azophor red
azo fuchsin
ponceau G
scarlet MOO
scarlet 2R
ethyl eosin
red violet 5R
black NBR
benzyl violet
propyl red
fast red
iodine violet
alizarine yellow 6
aurin
janus yellow
gallein
coerulein MS
direct green
fast green FCF
ponceau B
crocein

*Miscellaneous**Slightly active*

m-phenylenediamine
cyclohexanol
salicylaldehyde
penta-erythrityl bromide

2,3,5 triiodobenzoic acid
3,5 diiodo-2-hydroxybenzoic acid
acetylsulfanilamide 2,4 naphtho-
quinone

Inactive

p-aminophenol
diphtheria toxoid
diphtheria antitoxin
o-phthalonitrile
rotenone
cube root
naphthylmethylether
thiocoumarin
xanthone
azobenzene
p-nitroanisole
n-nitrosodiphenylamine

o-bromophenol
orcinol
ethyl carbamate (curcthan)
chlorohydroquinone (practical)
benzamide
triacetoneamine hydrate
thioacetamide
bromohydroquinone (practical)
toluhydroquinone
3,4-diaminotolulene (practical)
p-chloroaniline
alloxin chlorohydrate

Miscellaneous—Continued

hydroazobenzene	2,4,6-tribromophenol (practical)
plasmochin	formalide
saccharin	p-bromobenzoyl chloride
thymol	1,4-dihydroxybutane
chlorthymol	glycerolphenyl ether diacetate
phosphine	diisophorone
imidiazol	citrinin
2-4 dihydroxybenzoic acid	2 amino 9 phenoacridine
o-phenylenciamine	picrochrome

The diphtheria toxoid and antitoxin, tried because of their alleged efficiency in leprosy (17), were undoubtedly inactivated by the autoclave.

Briefly summarized, it is apparent that several widely diverse drugs inhibit the growth of tubercle bacilli *in vitro*. It may be important that several of those tried are probably not classical antiseptics, which act through complete chemical or physical destruction of the microorganism, but appear to resemble the newer bacterial chemotherapeutic agents whose effect is more subtle. This may be interpreted as indicating that the tubercle bacillus is susceptible to agents which need not necessarily destroy normal tissues, and, therefore, allows hope for a clinically effective agent. Also, it seems obvious that the waxy capsule is not necessarily a barrier to the action of lethal bactericidal agents.

IN VIVO TRIALS

Agents which inhibited the growth of tubercle bacilli in the test tube in 10 mg. per cent or less were tried in tuberculous guinea pigs, in so far as quantities sufficient for adequate testing were available. The compounds were given to young guinea pigs (weight about 300 g.) either by subcutaneous or intraperitoneal injection or mixed in their food or drinking water. The food was a prepared rabbit ration⁴ supplemented by greens once a week. When drugs were incorporated in it, the product was passed through a coarse grinder to allow better mixing and, therefore, more complete consumption of the drug. After two to five days of administration of the drug, the treated guinea pigs, together with the controls, were injected intraperitoneally or subcutaneously in the groin, with a suspension of 0.1 to 1 mg. of the 0-28 strain of tubercle bacilli. At death, examination was made for gross lesions, from which smears were made. When gross lesions were absent, or only suspected, smears were made from appropriate regions, including especially the regional lymph nodes. Intercurrent disease was responsible for the death of several guinea pigs, but four weeks after inoculation, the tuberculous lesions were normally large enough to insure accurate diagnosis. Animals dying earlier than this were discarded. From 2 to 75 medicated guinea pigs, with from 3 to 8 untreated controls, were used for each drug or combination of drugs studied. The larger number of guinea pigs was made up of several small groups of animals, run at different times, and seldom exceeding 8 guinea pigs each. Treatment was continued in most instances until the death of the animal. When

⁴ Purina Rabbit Chow.

TABLE 1

NUMBER OF GUINEA PIGS	DRUG	DOSAGE AND ROUTE	RESULT	REMARKS
4	Phenothiazine	$\frac{1}{2}\%$ in diet	No effect	
6	Dichlorosulfanilamide	12 to 25 mg. subcut. or orally, daily	No effect	
33	Butadiene monosulfone	25 to 50 mg. subcut., or 1% in diet or water	No effect	
4	Phenothiazone	$\frac{1}{2}\%$ in diet	No effect	
4	Thionol	$\frac{1}{2}\%$ in diet	No effect	
21	Sulfadiazine	$\frac{1}{2}\%$ to 1% in diet	No effect	
10	Sobisminol	$2\frac{1}{2}\%$ in water	No effect	
4	Santicizer 1H	$\frac{1}{4}$ to $\frac{3}{4}\%$ in diet	No effect	
4	Santicizer 8	$\frac{1}{4}$ to $\frac{3}{4}\%$ in diet	No effect	
10	Santicizer 9	$\frac{1}{4}$ to $\frac{3}{4}\%$ in diet	No effect	
10	Santicizer 10	$\frac{1}{4}$ to $\frac{3}{4}\%$ in diet	No effect	
10	Promin	$\frac{1}{4}$ to $\frac{3}{4}\%$ in diet	No effect	
4	Ethyl chaulmoograte	$\frac{1}{2}\%$ in diet	No effect	
4	Phenazine	$\frac{1}{2}\%$ in diet	No effect	
4	Sulfazoacridine	1% in diet	No effect	
3	Methyleneazur C	1% in diet	No effect	
2	Azur 1	20 mg. intraperitoneally daily	No effect	
2	Azur A French	20 mg. intraperitoneally daily	No effect	
11	o-Hydroxybenzal-sulfanilamide	2% in diet	No effect	
3	Sulfazoacriflavine	1% in diet	No effect	
3	Diphtheria toxoid	subcutaneously	No effect	
3	Diphtheria antitoxin	subcutaneously	No effect	
12	Butadiene monosulfoneamine	20 to 40 mg. subcut.	No effect	
4	Monomethyl butadienemonosulfone	10 mg. subcut. daily	No effect	
4	Dimethyl butadienemonosulfone	10 mg. subcut. daily	No effect	
8	Sulfolanylsulfanilamide	2.5 mg. subcut. or $\frac{1}{2}\%$ in diet	No effect	
75	Neosynephrine sulfathiazolate	10 to 50 mg. subcut. daily; and $\frac{1}{2}$ to 2% in diet	Questionable retardation in some animals	
6	10-Methyl-3-6-aminoacridineazosulfanilamide	2.5 to 10 mg. subcut. daily	Inconclusive	Unsatisfactory; sloughs at site of injection; necessitated brief treatment

TABLE 1—*Continued*

NUMBER OF GUINEA PIGS	DRUG	DOSAGE AND ROUTE	RESULT	REMARKS
5	Neutral acriflavine	2.5 to 5 mg. subcut. daily	Inconclusive	Unsatisfactory; sloughs at site of injection; necessitated brief treatment
13	Acridine orange CI 788	2.5 mg. subcut. daily	Inconclusive	Unsatisfactory; sloughs at site of injection; necessitated brief treatment
5	Acriflavinesulfanilamide	5 mg. subcut. daily	Inconclusive	Unsatisfactory; sloughs at site of injection; necessitated brief treatment
3	Acetone	2 cc. of 25% solution intraperitoneally daily	Inconclusive	Abdominal adhesions
6	Acetone plus sulfadiazine	2 cc. of 25% solution intraperitoneally daily, plus 2% sulfadiazine in diet	Inconclusive	
27	Diazone	0.75% in diet	Questionable retardation	Absent or minimal lesions in a few animals
8	Sulfadiazine plus zephiran	1 to 2% in diet 1:1000 to 1:4000 in drinking water	No effect	
19	Sulfadiazine plus propylene glycol	1 to 2% in diet 2.5 to 10% in drinking water	Questionable retardation	Absent or minimal lesions in a few animals
2	Cyclohexanol	40 mg. intraperitoneally daily	No effect	
5	Salicylaldehyde	40 mg. intraperitoneally daily	Inconclusive	

sloughing or subcutaneous fibrosis at the site of injection was produced, the course of treatment was limited to a few days or weeks, but the animals were observed for the usual periods. The results obtained are shown in table 1, in which "no effect" signifies that there was no detectable difference between control and treated animals.

It is seen that most of the compounds exhibiting bactericidal power *in vitro* were ineffective *in vivo*. Ethyl chaulmoograte was totally ineffective, and the acridine compounds produced only a very questionable improvement. It was impossible to obtain enough of the latter compounds to make adequate trials

by oral administration, and the irritating nature of the products limited their parenteral use to insufficient periods for complete assessment. Neosyneprine sulfathiazolate appeared to produce considerable retardation of the tuberculous changes in several animals, but this could not be confirmed on further trials. The combination of sulfadiazine and a solvent (acetone or propylene glycol) was interesting as retardation of the tuberculous lesions (but not enough to suggest clinical usefulness) was produced in some animals. The deterrent effect of diasone on the disease appeared to be only slight under the conditions of these experiments. The drug "promizole" could not be obtained for comparative testing.

The beneficial results obtained have all been characterized as retardations of the disease and not as cures, although in occasional animals all lesions appeared to have been totally suppressed. In control animals there was also, occasionally, marked suppression of the disease. The more striking results of other investigators may be due, in part, to the use of much smaller inocula of tubercle bacilli and older, and hence more resistant, guinea pigs.

CONCLUSIONS

1. Of 300 compounds tested *in vitro* as possible chemotherapeutic agents against *Mycobacterium tuberculosis var. hom.*, 39 of the more promising were tested in guinea pigs inoculated with tubercle bacilli.

2. Although slight and irregular suppression of the infection occurred with neosyneprine sulfathiazolate, diasone and a combination of sulfadiazine and propylene glycol, in no case did this appear adequate to justify clinical trials.

CONCLUSIONES

1. De 300 compuestos comprobados *in vitro* como posibles elementos quimioterapéuticos contra el *Mycobacterium tuberculosis var. hom.*, 39 de los que prometían más fueron comprobados en cobayos inoculados con bacilos tuberculosos.

2. Aunque el sulfatiazolato de neosinefrina, la diasona y una combinación de sulfadiazina y glicol de propileno, obtuvieron una leve e irregular supresión de la infección, en ningún caso pareció la misma adecuada para justificar ensayos clínicos.

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SULFADIAZINE IN EXPERIMENTAL TUBERCULOSIS¹

C. RICHARD SMITH AND FRANK W. OECHSLI

In the search for a chemotherapeutic agent against tuberculosis sulfadiazine recommends itself for trial because of an unusually low toxicity. Smith, Emmart and Westfall (1) noted inhibition of tubercle bacillus cultural growth by sodium sulfadiazine at a concentration of 10 mg. per cent. More effective were the three compounds, diaminodiphenylsulfone, diaminodiphenylsulfoxide and sulfathiazole; while less effective were phosphonilic acid and promin. The same authors treated infected guinea pigs by mouth for thirty days with 5 different drugs. Animals showing best survival and least disease at 107 days were those treated with diaminodiphenylsulfone, promin and sulfadiazine. Diaminodiphenylsulfone was considered the most effective agent *in vivo* and *in vitro*. Sulfadiazine showed an effectiveness *in vivo* comparable to that of promin.

Feldman and Hinshaw (2), on the other hand, after trying out 6 different compounds on tuberculous guinea pigs, reported sulfadiazine to be ineffective in comparison with the 3 sulfones, 4-aminophenyl-5-amino-2-pyridalsulfone, 4-amino-4-dodocanoylamidophenylsulfone and promin. This study was quite different in nature, however, from the foregoing. Here the animals were infected six weeks prior to, and were tuberculous at the beginning of treatment. Treatment then continued twenty-six weeks before autopsy.

PLAN OF EXPERIMENT

Forty-eight guinea pigs were separated into two groups as follows:

- A. 24 animals infected with tubercle bacilli but not treated.
- B. 24 animals infected and treated with sulfadiazine.

Each group was composed of an equal number of males and females kept separately, 6 to a cage. The average weights were 494.4 g. for group A and 486.9 g. for group B.

Infection was by subcutaneous injection into the right flank with 1 cc. of a suspension containing 0.0001 mg. moist culture of virulent human tubercle bacilli (strain 88) three and a half to five weeks old.

The experiment was staggered over a period of twelve days, one male and one female from each group being inoculated each day and all subsequent examinations being staggered accordingly.

Drug treatment was started on the same day as infection, following an eight-day period of gradual acclimatization to the drug. The sulfadiazine powder was incorporated in the feed pellets in a concentration of 1.3 per cent according to the method of Feldman (3). The average daily intake of drug was estimated at 257 mg., equal to 524 mg. per kg.

The experiment was scheduled to run twenty-eight days.

¹ From the Barlow Sanatorium, Los Angeles, California.

Blood chemistry: Blood concentrations of free sulfadiazine were determined immediately prior to autopsy, that is, at the end of twenty-eight days between 8:00 and 8:30 in the morning. In 16 group-B animals the levels varied from 7.0 to 17.1 mg. per cent with an average of 12.2 mg.

Tuberculin tests: Intracutaneous injections were made with 0.1 cc. of 5 per cent OT. The reactions were graded according to Aronson (4). The results are shown in table 1.

Postmortem examination: One group-A animal was lost; one group-B animal died on the twelfth day and was excluded from the evaluation of results, one died on the twenty-second day but was included in the results. Those remaining were killed on the twenty-ninth day after infection.

There were 23 animals in each group suitable for disease evaluation. Gross estimates were made of size and numbers of lesions in the spleens and livers. Spleens, livers and tracheobronchial lymph nodes² were weighed. Weighed fractions of spleens and livers were ground up and cultured quantitatively in

TABLE 1
Reactions to 0.1 cc. of 5 per cent Old Tuberculin.

REACTION	2 WEEKS		3 WEEKS		26 DAYS
	Control	Treated	Control	Treated	Treated
Positive	10	2	23	4	12
Doubtful		4		8	7
Negative	13	17		10	3
Animals lost or dead....	1	1	1	2	2

serial dilution. The remaining portions of the organs as well as the tracheobronchial lymph nodes were preserved in Kaiserling's fluid for later gross and microscopic evaluation.

The data for each type of examination were placed in an array of increasing values. Spleens preserved in Kaiserling solution were arranged by direct comparison according to the amount of gross disease. Fresh tissue inspection determined the gross values for livers. Microscopic sections were arranged by direct comparison. In the case of tracheobronchial lymph nodes, the actual grams of tuberculous tissue were calculated from microscopically determined diameters of nodes and diseased tissue and the lymph node weights.³ Total numbers of live tubercle bacilli present in each organ were estimated from colony counts of the cultured fractions. All disease evaluations were made without knowing the true designation of the organ or tissue, that is, without prejudice.

² The amount of disease in the tracheobronchial lymph nodes was considered a measure of lung infection.

³ These calculations were based on the assumption that the lymph nodes and their diseased regions were spherical. This is only partly true and the calculations therefore only approximate.

Results: The treated animals had less tuberculosis than the controls, in every case. All control guinea pigs were grossly positive for tuberculosis in livers and spleens; all were microscopically positive in the spleens and tracheobronchial lymph nodes, all positive in the livers with one exception; all control spleens and livers were positive by culture. Three of the treated animals were completely free of disease grossly and microscopically. The spleens were negative to gross examination in 22, to gross and microscopic examination in 10 and to cultural examination in 2 guinea pigs. The livers were negative to gross inspection in 20, gross and microscopic examination in 14 and to culture in 6. The tracheobronchial lymph nodes were microscopically negative in 12 cases.

The numbers of tubercle bacilli cultured from the control spleens and livers were, on the average, about fourteen times greater than those cultured from the treated organs. Thus the mean number of bacilli in the treated spleens was 248,000 with extremes of none and 3,168,000; the mean number in the control spleens was 3,371,700 with extremes of 783,000 and 50,350,000. The mean bacillary count for treated livers was 255,000 with extremes of none and 3,689,000. The mean for control livers was 3,724,862 with extremes of 47,000 and 29,380,000.⁴

The calculated grams of tuberculous tissue in the tracheobronchial lymph nodes were on the average 400 times greater in the control than in the treated animals. The mean value for the former was 0.1998 grams with extremes of 0.0002 and 0.7080; that for the latter was 0.0005 grams with extremes of none and 0.0030 grams.⁴

No attempt was made to obtain absolute figures for the results of gross and microscopic examinations in the spleens and livers. The positive organs were designated minimal, moderately advanced and far advanced according to the relative amount of disease. If the organs from the treated and control animals are arrayed separately as above, the median item from each group serves as a basis for comparison. Thus, for gross examinations, the median spleen of the treated group was negative, that of the control group showed perhaps half its Malpighian bodies enlarged to from 1 to 2 mm. and was rated as moderately advanced. The median treated liver was negative, that of the controls was estimated to have 150 surface lesions averaging 0.5 mm. in diameter and was classified as moderately advanced.

Microscopically, the median treated spleen was classified as minimal and only 2 or 3 of its Malpighian bodies showed epithelioid cell proliferation involving a small fraction of their areas. The median control spleen was rated as far advanced and showed almost complete epithelioid cell involvement of the majority of the Malpighian bodies with beginning caseation in the centres of several. The median treated liver was microscopically negative; the median control showed perhaps half of its portal spaces involved in epithelioid change, one-fourth of these having caseous centres, and it was rated as moderately advanced.

⁴ The distribution of these data is irregular.

DISCUSSION

Objectivity in disease evaluation was aided by coded labeling of preparations for examination, by the direct comparison technique and by the use of measurements and weights in lymph node calculations.

We did not attempt to obtain a single figure representing disease extent and severity. Such procedure is not entirely satisfactory. Moreover, the difference between the treated and control groups was so nearly complete according to the several measures of disease that a marked chemotherapeutic effect cannot be questioned.

Of interest in connection with the evolution of disease evaluation methods is that the gross rating of splenic disease agreed exactly with the predominance of evidence from all measures.

The estimated numbers of tubercle bacilli in the spleens and livers are parallel to the disease evaluations with few exceptions. The obvious implication is that this drug prevents disease development by inhibiting the multiplication of bacilli in the animal tissues.

The delayed appearance of tuberculin sensitivity in the treated guinea pigs is likewise parallel to postmortem findings. This phenomenon was observed in a previous study (5). There is evidence that the speed of the evolution of allergy is dependent on the number of tubercle bacilli entering the tissues (6). Thus it is indicated that the time required for the elicitation of a positive tuberculin reaction may within limits be used as an inverse measure of the multiplication of tubercle bacilli in the infected animal and, it follows, of the resultant disease development.

It is a question as to whether human trials of sulfadiazine treatment should be recommended. That we found invariable inhibition of disease in a fairly large number of animals is suggestive. Smith, Emmart and Westfall, however, whose experience with sulfadiazine agrees in general with ours, preferred to look toward the preparation of less toxic derivatives of diaminodiphenylsulfone. That Feldman and Hinshaw found sulfadiazine "ineffective" in the treatment of already established animal tuberculosis is certainly not encouraging in the consideration of human disease treatment. These authors, too, were more impressed by the sulfone type of compound. On the other hand, the widespread use and familiarity with sulfadiazine along with its relative safety and low proportion of side reactions are in favor of clinical trial.

SUMMARY

1. Following infection with tubercle bacilli, sulfadiazine treated guinea pigs were slower in the development of allergy than the controls.

2. Animals treated with sulfadiazine for four weeks following infection invariably had less tuberculosis than the controls. About one-half of the spleens, livers and tracheobronchial lymph nodes from the treated animals showed no tuberculosis on microscopic examination.

3. There were about fourteen times as many tubercle bacilli in the spleens and livers of the control animals as in the treated animals.

4. The slower evolution of allergy and the lesser disease in the treated animals is probably a result of drug inhibition on multiplication of tubercle bacilli.

SUMARIO

1. Después de ser infectados con bacilos tuberculosos, los cobayos tratados con sulfadiazina mostraron un desarrollo más lento de alergia que los testigos.

2. Los animales tratados con sulfadiazina durante cuatro semanas consecutivas a la infección, mostraron invariablemente menos tuberculosis que los testigos. Aproximadamente la mitad de los bazos, hígados y ganglios linfáticos traqueobronquiales de los animales tratados, no revelaron tuberculosis al microscopio.

3. Encontráronse aproximadamente 14 veces más bacilos en los bazos e hígados de los testigos que de los animales tratados.

4. La evolución más lenta de la alergia y la menor patología en los animales tratados representan probablemente el efecto inhibitor de la droga sobre la multiplicación de los bacilos tuberculosos.

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ABST. No. 1

Emphysema.—Emphysema is a progressive and incapacitating disease. The majority of cases diagnosed postmortem are not recognized during life. By emphysema is meant a chronic vesicular or hypertrophic condition of the lungs. Acute emphysema, senile emphysema and localized emphysema are probably separate and distinct entities not discussed in this paper. The normal lung lobule or air sac consists of an alveolar duct opening into the atrium, around which are placed the alveoli. In health there is a sudden transition from narrow alveolar duct to wide atrium, so that the inspired air may be thrown as a jet into the more remote parts of the terminal segment. The conclusion is drawn from various observations that the emphysematous lung is deformed in at least three ways. First, many lobules or air sacs are misshapen and the alveolar ducts are dilated, so that air is no longer thrown into the atrium as a jet. Second, the septa between alveoli may disappear so that the supporting framework of the air sac may be lost. Third, the amount of air in the lungs is usually increased, but this increase is not proportionate to the severity of the disease, nor is the volume of the emphysematous lung at rest ever as great as the volume of a normal lung in full inspiration. Thus, whatever may be its microscopical appearance, the lung as a whole in emphysema is not overstretched or overdistended any more than a normal lung is overdistended or overstretched when a breath of moderate depth is taken. The author states that, in his opinion, it is the loss of elasticity of the lungs, coming early and complete that brings about the changes seen in emphysema. The

method he used to determine the elasticity of the lung in pulmonary emphysema was the measurement of the intrapleural pressure, which is a direct measure of the tension or elastic recoil of the lung. In emphysema the intrapleural pressure is not always negative as it is in health; even at the end of a full inspiration the intrapleural pressure may be the same as that of the atmosphere, and it is not altered when the lung is collapsed by a pneumothorax. These phenomena can only mean that the elasticity of the lung in emphysema may be entirely lost at a comparatively early stage of the disease. Thus, the loss of pulmonary elasticity in emphysema could be the direct cause of expansion of the thoracic cage, rather than vice versa. Loss of elasticity could also explain the real overdistension of air sacs, with bulla formation which occurs on the surface of the lung. With loss of elasticity the expanding force is no longer equally distributed. In fact, the greatest expansion occurs at the surface of the lung. Thus, with each inspiration the superficial air sacs are stretched and strained to a greater extent than the air sacs deep in the lungs, and, with this process going on for months and years, it is easy to understand the formation of bullae on the surface of the organ. It is agreed that the pulmonary vascular bed is diminished in emphysema and that the work of the right ventricle may be increased, but this does not mean that the total blood flow through the lung is diminished. Microscopically the changes in the lung are uniform throughout the lung, but the dilatation of air sacs is most conspicuous at the periphery. The visceral pleura is thin, flimsy and atrophic.

There is usually a moderate degree of kyphosis, involving all the thoracic vertebrae, and the ribs are widely spaced and run horizontally. By far the most important disturbance of function in emphysema is an inability to ventilate the blood, and this is usually apparent many years before the patient reaches the pathologist. The simplest way to measure deficient ventilation in the lungs is to analyze the arterial blood. The important changes in the blood which occur in emphysema are a gross deficiency in both oxygen absorption and CO₂ elimination. The defect seems to lie in deficient ventilation of the alveoli rather than in any barrier between the alveolar air and the blood. The author rules out the following causes of impaired hemo-respiratory exchange: (1) diminution in vital capacity; (2) a barrier to the transfer of gases across the pulmonary epithelium; (3) insufficient functioning lung due to alveolar destruction; (4) diminution in pulmonary blood flow; (5) defective ventilation of the pulmonary lobule; (6) increase in the volume of lungs; and (7) increase in the physiological dead space. The author concludes that the cause of impaired hemo-respiratory exchange in emphysema is the formation of a pathological respiratory dead space, consisting of bullae and other air sacs which are not in contact with the pulmonary circulation. The cause of dyspnea in emphysema is stimulation of the respiratory centre by the CO₂ retained in the blood. In the absence of bronchospasm there is no orthopnea because there is no pulmonary congestion. In attempting to analyze the physical signs in emphysema it is pointed out that the diaphragm, because it is no longer pulled upwards by the lungs, descends and becomes less convex, and its movements on inspiration are greatly diminished. The intercostal muscles which are primarily concerned with moderate inspiration will also be unable to function properly. To expand the chest further the accessory muscles will have to be used, particularly the pectorals, and these raise the front of the chest as a whole in a "heaving" manner. Normally, expiration is largely, if not wholly, a passive act; the thoracic cage is

pulled inwards by the elastic recoil of the lung. With loss of elasticity there must be a loss of elastic recoil, so that if the lung is to be deflated it has to be squeezed. Thus, the accessory muscles of the abdominal wall come into play in expiration. The overdistension of superficial air sacs is presumably the cause of the remarkable hyperresonance of the percussion note. Furthermore, with each inspiratory effort the anterior chest wall is pulled outwards and upwards as a whole, and much of this force must be expended on pulling the lung into the pleural sinuses, thus filling the potential gap between the chest wall and the heart. This explains the absence of apical impulse, loss of cardiac dullness, distant heart sounds and loss of liver dullness. The three important factors leading to the formation of the barrel-shaped chest are: (1) the inspiratory position of the chest; (2) the expansion of the lung between the heart and the sternum; and (3) the dorsal kyphosis throughout the thoracic vertebrae. Almost all cases of emphysema have a long-standing history of chronic bronchitis or asthma, or both. The effects of cough and bronchial spasm on the lung and its mechanism are therefore of primary importance in any discussion on the etiology of this disease. During the mechanism of coughing the lung is compressed and not in any sense distended. This building up of pressure followed by its sudden release must mean increased stress and strain on all the structures involved, especially on the alveolar walls, which are not robust and through which passes this wave of pressure change. A chronic bronchitic may cough scores of times a day, and it seems reasonable to suppose that this type of stress and strain repeated over many years could in time produce the loss of elasticity and degenerative changes observed in the alveolar walls. In asthma there is the same degree of change in intraalveolar pressure as in coughing. The author concludes that almost all patients with emphysema suffer from chronic bronchitis or asthma and, thus, the explanation of the pathogenesis of emphysema lies in the effects of those two diseases on the lungs. There still remains to be ex-

plained the unusual case of emphysema with no previous history of asthma or chronic bronchitis. The author can only suggest that, very rarely, the stress and strain on the lung which occurs with ordinary breathing may be sufficient to destroy its elasticity. The author reviewed 72 cases diagnosed on the postmortem table as generalized hypertrophic emphysema. A history of chronic cough was given in 94 per cent and in a quarter of these it was associated with mild or severe asthma. Dyspnea on exertion was present in 78 per cent of the cases. In the majority of the cases, however, the physical signs of emphysema were not observed. In 35 per cent there was enough evidence to suggest an "emphysematous chest," but in only 13 per cent could this evidence be more complete. Thus, the author suggests that a more reliable guide to a diagnosis of emphysema than the physical signs is a history of chronic cough or asthma, associated with dyspnea on exertion. Thus, investigation of a series of 25 patients who gave such a history, and in whom no cause of dyspnea other than emphysema could be discovered, led to the findings that in 92 per cent of them two or more of the physical signs of emphysema were present. In 90 per cent expiration was prolonged, and only 44 per cent showed the traditional picture of emphysema. In the author's opinion the diagnosis of emphysema should only be considered certain when dyspnea on exertion, of insidious onset, not due to bronchospasm or left ventricular failure, appears in a patient who has some of the physical signs of emphysema together with chronic bronchitis or asthma. Treatment of emphysema is essentially symptomatic, as elastic tissue cannot regenerate and nothing can restore the structure of the lungs. Ephedrine not infrequently relieves the dyspnea of emphysema. Respiratory exercises designed to teach the patient to deflate the lung and to increase the use of the diaphragm are important. A well-fitting abdominal belt will also raise the diaphragm by increasing the intraabdominal pressure. When heart failure supervenes, oxygen should be given. Recovery from heart failure in

emphysema is uncommon.—*Emphysema of the Lungs*, R. V. Christie, Part I, *Brit. M. J.*, January 22, 1944, 1: 105; Part II, *Brit. M. J.*, January 29, 1944, 1: 143.—(D. H. Cohen)

Emphysema.—Two reasonable hypotheses exist for the development of hypertrophic emphysema: (1) the theory of compensatory distension and (2) the theory of obstruction. The former reasons that, where alveoli are destroyed by disease, either there ensues a contraction of the thoracic cage or an expansion of the remaining distensible structures or both. The latter theory postulates that, in any disease in which the smaller bronchi and bronchioles are chronically obstructed, as in asthma or chronic bronchitis, there is a difference in the degree of obstruction in the various bronchioles. Therefore, during inspiration, more air will enter the tube of wider calibre than will enter the narrower tube. Hence, alveoli communicating with the less obstructed tubes will inflate more quickly than will the others. In order to fill the less normal alveoli and thus achieve the necessary ventilation, the more normal alveoli will overdistend. This irregularity in distension will produce ultimate loss of elasticity and eventually hypertrophic emphysema.—*The Mechanism of Hypertrophic Pulmonary Emphysema*, I. Gordon, *Dis. of Chest*, May-June, 1944, 10: 180.—(K. R. Boucot)

Emphysema and Lymphoid Hyperplasia.—A case of increasing shortness of breath over a period of three years in a thirty-one year old white male is reported. The patient had been treated for bronchial asthma without success. Physical examination was negative except for hyperresonance with almost complete absence of breath sounds and for marked dyspnea. Roentgenographic examination revealed widely disseminated, healed tuberculosis throughout both upper lobes with some fibrosis and a generalized emphysema. Bronchography and bronchoscopy were negative. The dyspnea and emphysema became increasingly severe and the patient finally died in asphyxia. At autopsy, which was limited to

the chest, emphysema was present throughout the lungs. Masses of lymphoid tissue were present in the walls of small bronchi and bronchioles, frequently bulging into and forming polypoid projections in the lumina, thus producing varying degrees of narrowing. The lungs resembled those of the rabbit or guinea pig. The thymus and mediastinal lymph nodes were normal. The origin and nature of the condition is unknown.—*Bronchiolar Lymphoid Hyperplasia as a Cause of Emphysema: Report of a Case, W. W. Brandes, R. A. Cook & M. P. Osborne, Arch. Path., November, 1943, 36: 465.*—(D. G. Freeman)

Bronchial Asthma.—Two cases of bronchial asthma resulting from sulfonamide sensitivity are reported. The first patient developed a status asthmaticus on the tenth day of sulfathiazole therapy for a chronic nasal infection. The patient did not become symptom-free for an entire week. After another week he voluntarily ingested 2 g. of sulfathiazole. After some initial symptoms he developed an attack of bronchial asthma which started four hours after the intake of the drug and lasted for twelve hours. His vital capacity dropped from 4,000 to 2,150 cc. The number of eosinophils showed an initial rise to 13.2 per cent followed by a drop to 4.1 per cent and another rise to 29 per cent after thirty-five hours. This patient had no previous history of an allergic manifestation nor was there a history of an allergic condition in his family. The second patient gave a history of infantile eczema at the age of five years. At the age of thirty years she developed allergic manifestations including asthma due to wheat and house dust. Four years later she took sick with pneumonia and sulfadiazine therapy was given. On the ninth day of chemotherapy a rash was noticed and cyanosis and dyspnea became pronounced. Within twenty-four hours after the discontinuation of the sulfadiazine medication the condition improved markedly. About a year later she received a single dose of 0.5 g. of sulfadiazine for an upper respiratory infection with sore throat. Three hours later she developed a typical asthmatic

attack. A trial dose of 0.5 g. of sulfadiazine was voluntarily ingested a year later. There was a drop of her vital capacity from 3,200 to 2,300 cc. but no asthmatic attack developed.—*Bronchial Asthma as a Manifestation of Sulfonamide Sensitivity, T. G. Randolph & F. A. Rawling, J. A. M. A., September 16, 1944, 126: 166.*—(H. Abeles)

Silicosis.—A fifty-five year old man offered as chief complaint shortness of breath. Roentgenographic examination of the chest showed enlarged hilar nodes, mottling and accentuated markings. The radiological diagnosis was pneumoconiosis. The occupational history revealed that the patient had worked as unloader of wheat in a very dusty atmosphere for eight years. The silica content of the dust was 9.96 per cent. Reexamination of the patient after two years showed progression of the fibrotic process although exposure to the wheat dust had been discontinued.—*A Case of Silicosis Caused by Wheat Dust, T. F. Heatley, D. Kahn & C. R. Rex, J. A. M. A., April 1, 1944, 124: 980.*—(H. Abeles)

Bagassosis.—Seven cases of bagassosis, a respiratory illness occurring in people working with bagasse (the product remaining after extraction of sugar from sugar cane), had been reported. Another 11 cases of bagassosis were observed, 2 of which are described in detail. All patients were men; 6 were white, 5 were Negroes. The average age of the patients was twenty-seven years. Exposure to bagasse had taken place from three weeks to two years. Early symptoms were cough and dyspnea. Four patients had hemoptysis. The cough became productive of scant whitish sputum. The patients ran an intermittent fever from 99.8° to 101.2°F., through three or four weeks. Tachycardia was observed in 4 cases. Impaired resonance of the lungs and diminished breath sounds were found in 4 patients, râles in 8. Roentgenological examination revealed miliary mottling throughout both lungs, most dense in the hilar areas. Ten patients developed leucocytosis with 73 to 90 per cent

polymorphonuclear cells. The red cell count and the hemoglobin were usually found increased. The sedimentation rate was increased. Intracutaneous tests with extracts of bagasse were done; allergy could not be proved. Bagasse contains 5 to 7 per cent silica; however, the short incubation period and the short course of the disease speak against silicosis. Evidence from histological study of involved areas of the lung indicates the presence of bagasse dust with a severe and unusual cellular reaction, the nature of which has not yet been established.—*Bagasse Disease of the Lungs*, W. A. Sodeman & R. L. Pullen, *Arch. Int. Med.*, May, 1944, 73: 365.—(G. C. Leiner)

Pulmonary Edema.—The incidence of pulmonary edema following exposure to toxic gases has risen due to the increase in industrial production. The most common noxious agents are oxides of nitrogen, phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, methyl bromide, chlorine, cadmium and dust from certain alkaloids. A method is described which was used for the prevention and treatment of pulmonary edema. It consists of absolute bed-rest and the immediate administration of oxygen under atmospheric pressure with a provision for expiration against calibrated resistance of from 1 to 6 cm. of water pressure. One starts with 1 cm. of water pressure and increases it to 6 cm. of water pressure within five to ten minutes. Oxygen administration is usually kept up from one to three hours and then it is gradually discontinued. In cases with actual pulmonary edema the recommendation of Richards was followed and a 1 to 100 solution of epinephrine was administered by the oral nebulizer either prior or during the administration of oxygen. The epinephrine can be used continuously with the oxygen or at intervals. This method was used for the treatment of pulmonary edema due to noxious gases in 316 cases during the past year and a half. In some cases the oxygen-helium mixture was used with significant benefit. The routine, however, was to use 100 per cent oxygen to

which air could be added. Not more than 25 per cent of air should be added. The hacking cough caused by the oxygen treatment was controlled by one or two swallows of milk. The described form of therapy when used in the incipient stage of pulmonary edema will frequently prevent its advancement to a serious stage. Morphine, venesection or other forms of treatment are of no value or even contraindicated.—*Pulmonary Edema*, J. M. Carlisle, *J. A. M. A.*, December 11, 1943, 123: 947.—(H. Abeles)

Spontaneous Pneumothorax in Asthma.—Spontaneous pneumothorax occurred as a complication of bronchial asthma in 2 cases. This is a potentially fatal complication of bronchial asthma. Its diagnosis is extremely difficult in certain cases. This complication should be considered in every case of intractable or atypical asthma. Spontaneous pneumothorax and bronchial asthma are probably sometimes associated with mediastinal and interstitial emphysema. (Author's summary.)—*Spontaneous Pneumothorax Complicating Bronchial Asthma. Report of Two Cases and Consideration of Possible Mechanisms Involved in Its Production*, M. Troubridge, Jr., *Arch. Int. Med.*, June, 1944, 73: 460.—(G. C. Leiner)

Bilateral Spontaneous Pneumothorax.—A twenty-seven year old soldier gave a history of a sudden agonizing pain in the left side of his chest. The previous day he had done some heavy lifting but the pain occurred while resting in bed. Physical and radiological examinations established the diagnosis of spontaneous pneumothorax on the left side. The patient improved on codeine and pentobarbital sodium therapy. Ten days later he experienced a sudden pain in the right side of his chest. He was in acute distress but his condition improved temporarily following decompression on the right and oxygen therapy. Radiological examination revealed marked collapse of the right lung and partial reexpansion of the left lung. On the eleventh day of hospitalization the patient became

restless, the respiratory rate dropped from 35 to 18 and the respiration was of Cheyne-Stokes character. He died on the same day in deep cyanosis. In the twenty-four-hour period prior to his death he had received a total amount of 0.1 g. of morphine. The post-mortem diagnosis was bilateral pulmonary atelectasis caused by bilateral spontaneous pneumothorax. A small tear was found in the visceral pleura on the left, none could be demonstrated on the right. The heart was displaced to the right, the right ventricle and auricle were much distended. No evidence of tuberculosis was found.—*Bilateral Spontaneous Pneumothorax*, A. C. King & M. Benson, J. A. M. A., July 15, 1944, 125: 782.—(H. Abeles)

Spontaneous Pneumothorax.—The 33 cases of spontaneous pneumothorax observed were thus subdivided: spontaneous pneumothorax probably due to tuberculosis, 24.2 per cent; spontaneous pneumothorax definitely due to tuberculosis, 33.3 per cent; spontaneous pneumothorax due to bronchial asthma and emphysema, 11.1 per cent; spontaneous pneumothorax due to other pulmonary conditions, 18.1 per cent. The remaining 12.1 per cent were observed in young persons without pulmonary disease and without previous history.—*Considerazioni critiche su 33 casi di pnx. spontaneo*, Marfori & Austonu, *Il Policlinico*, 1939, 46: 113.—(G. Simmons)

Spontaneous Pneumothorax.—In a brief survey of the literature Itard is credited with first use of the term "pneumothorax" in 1803. His and subsequent work indicated that it occurred spontaneously mainly in tuberculous patients. But in 1887 Hall suggested its occurrence in nontuberculous individuals and in 1942 Ornstein and Lercher reported 58 cases in apparently healthy persons. Chief theories as to its causation are: (1) rupture of a pleural tuberculous focus, (2) rupture of a pleural adhesion, (3) rupture of an emphysematous bleb and (4) presence of a pleural defect. In 50,000 examinations of the chest reviewed by Santos and Tanchonco an inci-

dence of 0.11 per cent was noted, males predominating two to one. Ehrlich and Schomer classified spontaneous pneumothorax thus: (1) the open type with air freely entering and leaving the pleural cavity through a rupture of the lung, (2) the closed type with only a transient admission of air into the pleural cavity before sealing of the rupture and (3) the valvular type with air entering the pleural space during inspiration and being trapped there to cause a tension pneumothorax. McGuire and Bean described a fourth in which air escaped from ruptured alveoli or bronchi into pulmonary interstitial tissue. Cardinal symptoms are chest pain and dyspnea but shock and cyanosis may be present in tension pneumothorax. Diagnosis may be made on physical examination alone but radiographic confirmation is advisable. A period of bed-rest with subsequent avoidance of physical efforts, especially exertion with a closed glottis, is given as the treatment of choice; aspiration of air should be resorted to only in the presence of definite tension. X-ray examination to rule out underlying pulmonary disease is advised before discharge of the patient. The authors report 5 cases of spontaneous pneumothorax, all in apparently healthy members of military units. A tuberculous focus was not found in any one of the 5; so it was assumed that a ruptured emphysematous bleb was the etiological agent in all. Four gave a history of exertion at the time of collapse while the fifth was at complete rest. All were recommended for reclassification as regards military service and it is suggested that every person who undergoes spontaneous pneumothorax be so reclassified.—*Spontaneous Pneumothorax*, G. H. Stein, E. B. McConkie & A. J. Kuhn, *War Med.*, September, 1943, 4: 324.—(L. R. Roll)

Bronchial Carcinoma.—Carcinoma of the lung ranks next to carcinoma of the colon in frequency in men. The first signs or symptoms of bronchial carcinoma consist of any change from normality, and the commonest of these is cough. At first the cough is usually dry and unproductive and is dismissed

as "smoker's cough," "bronchial catarrh" or some such vague condition. By far the most important group of symptoms arises from the infection that sooner or later follows upon bronchial obstruction. It often begins as an apparently straight-forward attack of pneumonia or "influenza" but significantly resolves incompletely or not at all. "Delayed resolution," "unresolved pneumonia," recurrence of smouldering sepsis in part of a lung, particularly in a patient of middle age, should always give rise to a strong suspicion of malignant lung disease. General deterioration of health, loss of weight and loss of strength are usually the signs of approaching death and, so far as operability is concerned, their presence almost always means that the case is unsuitable. Once the presence of a growth of the lung is suspected, good chest radiograms should be taken. Any suspicious shadow revealed will demand further investigation by bronchoscopy. During bronchoscopy a piece of tissue should be removed for biopsy. The only cure for bronchial carcinoma is by operation. Operability at present is rather less than 10 per cent. The operation of choice is pneumonectomy. The recurrence rate after only lobectomy is unduly high. The operative mortality in this series was 29 per cent, but included were 3 cases over sixty years of age. Pneumonectomy performed properly for carcinoma in a patient under sixty should not carry an operative risk over 10 per cent, however. Of the 29 cases in this series, 8 died from operation, 7 from recurrences and 14 are alive and well. The disability from a successful pneumonectomy is negligible. Of the 21 cases surviving operation, all but one had sound healing and only one needed a thoracoplasty. All of the successful cases returned to their former occupation which in some cases was quite arduous. The main complaint is occasional dyspnea on overexertion.—*Surgical Treatment of Bronchial Carcinoma*, B. C. Brock, *Brit. M. J.*, August 28, 1943, 2: 257.—(D. H. Cohen)

nomata of the lung described under a variety of names, but always with the idea that the primary foci are the septal cells lining the pulmonary alveoli. Unfortunately there is no agreement as to just what kind of cells line the pulmonary alveoli. Current views range all the way from a continuous layer of epithelial cells; an epithelial but discontinuous layer; that the cells are not epithelial but mesenchymal in origin; and that there are both epithelial and mesenchymal cells present. One of the most conspicuous and consistent findings in any chronic inflammatory or fibrotic process of the lung is the presence of cuboidal epithelium forming a continuous lining of the alveolar septa or spaces in a fibrous tissue stroma. The histogenesis of the epithelium has two interpretations. The older and by far the more prevalent view is that the cells arise from former alveolar epithelium which has now resumed its embryonic appearance. The second view is that these cells do not originate from the septal cells but that they are outgrowths of the basal cells of the bronchiolar mucous membrane. In an effort to establish the histogenesis of these regenerated cells, a detailed review was made of 60 bronchiectatic lungs together with miscellaneous cases of tuberculosis, organizing pneumonia, interstitial pneumonia and lipoid pneumonia. The two most important and constantly observed changes relevant to the present discussion were (1) the frequent occurrence of metaplasia of the bronchial mucosa to a transitional or squamous cell type and (2) the presence of various amounts of granulation or fibrous tissue which consistently surrounded the involved smaller bronchi and their terminal ramifications, and the gradual merging of this tissue with the adjoining thickened alveolar septa. Throughout these areas, regular, low cuboidal or even attenuated epithelium lined the alveoli and the spaces within the granulation and fibrous tissue. On consecutive sectioning these lining cells were seen to originate in the mucosa of the bronchioles. Furthermore, since preoperatively lipoidol was instilled in all of the

Bronchial Origin of "Alveolar Cell Tumor."
—There is a small group of primary carci-

lungs, there were frequently seen large macrophages whose cytoplasm was distended with injected oil completely filling the alveoli lined by regenerated cuboidal cells. If the regenerated alveolar epithelium arises from septal cells, one would also expect these regenerated cells to show at least some degree of phagocytosis, since septal cells are known to be phagocytic. But none of the latter showed any evidence of phagocytosis. All available evidence substantiates the supposition that the source of the regenerated alveolar epithelium is the basal cell of the bronchioli and not the preëxisting cell which has now resumed its embryonic appearance. The microscopic findings from 6 cases of "alveolar cell tumor" of the lung are discussed in detail. All of these cases apparently showed many or most of the alveoli lined with cuboidal or columnar cells. Often the tumor cells lined only a portion and one side of an alveolus and then ended abruptly. *Conclusions:* Considerable evidence is presented to show that regenerated alveolar epithelium arises not from septal cells but from the basal cells of the bronchioles. On this basis alveolar cell tumors are also considered to arise from the basal cells of the bronchioles and not from septal cells. This is given additional support from a study of the pleomorphism of the more commonly observed bronchogenic carcinoma in which squamous or anaplastic cells and cuboidal or columnar cells are found side by side in the same tumor and even in the same microscopic field. It is believed that the parent cell in all cases of primary carcinoma of the lung is the basal cell of the bronchial or bronchiolar mucosa. The distribution of the subsequent tumor is dependent upon the further differentiation of the cells. If they are anaplastic or squamous, they will be either irregularly distributed throughout the lungs or will occupy the alveolar spaces just as does an inflammatory exudate in pneumonia. If they are cuboidal or columnar, they will regularly line the septa producing the well known alveolar arrangement. While only a few tumors are indisputably of one group or the other, there are many inter-

mediary transitions between the two. (With 3 plates).—*Bronchiolar Origin of "Alveolar Cell Tumor" of the Lung*, P. A. Herbut, *Am. J. Path.*, September, 1944, 20: 911.—(J. S. Woolley)

New Growths of Chest.—Neoplasms of the chest may be classified as follows: (1) tumors of the major bronchi, (2) tumors of the minor bronchi or periphery of lung, (3) anterior mediastinal tumors, (4) posterior mediastinal tumors, (5) rare mediastinal tumors, (6) tumors originating in the chest wall, (7) non-neoplastic tumors. Subdivisions under these main headings are presented. As diagnostic criteria, diagnosis by biopsy and cell study is recommended. Material may be obtained by endoscopy, lymph node removal, punch biopsy of the tumor proper, centrifuged material from pleural fluid or sputum. X-ray studies with flat plates, stereoscopy and fluoroscopy are recommended. Bronchography may be helpful. Tomography may demonstrate the relationship between the tumor and the bronchus. Diagnostic pneumothorax may differentiate pulmonary from mediastinal or thoracic wall tumors. Diagnostic pneumoperitoneum may distinguish between supra- and subdiaphragmatic lesions, including herniation. Deep X-ray treatment may help to differentiate the lymphoblastomata. X-ray studies of possible primary tumors may confirm suspicion of metastatic malignancies. Bronchoscopy and esophagoscopy may be diagnostic. Surgical exploration is warranted. Laboratory tests to rule out non-neoplastic diseases such as tuberculosis, leukemia, thyroid enlargement, etc. is important when indicated. Kymography and thoracoscopy may assist in the diagnosis of pulsating masses and pleural tumors, respectively. Symptoms and signs are of considerable significance. Thirteen case studies are presented.—*New Growths of the Chest*, C. W. Tempel, *Dis. of Chest*, July-August, 1944, 10: 277.—(K. R. Boucot)

Congenital Absence of Lung.—Authors here report 2 cases, one proved by exploratory

operation, and 38 other cases from the literature. There may be three types of this abnormality: (1) true aplasia in which there is no trace of lung, bronchus or vascular supply; (2) the bronchus is represented by a small outpocketing from the trachea but no lung tissue is present; (3) there is extreme hypoplasia, the bronchus is fully formed but is reduced in size and ends in a fleshy structure without lobes which lies within the mediastinum. The symptoms may be only dyspnea, cyanosis and harsh breathing; young patients usually do not develop so well or so rapidly as normal children do. Objectively there are found: asymmetry of the chest, scoliosis (either toward or away from the affected side), atrophy of muscles, displacement of heart and mediastinum toward the side of the absent lung, elevation of the diaphragm and narrowing of intercostal spaces. The percussion note may be dull or flat, or resonant from hypertrophy and emphysema of the other lung. Breath sounds are either absent or suppressed or bronchial for the same reason. Bronchoscopic studies reveal a block of the main stem bronchus a short distance from the carina provided there is a rudimentary main stem bronchus at all. Absence of a lung is not incompatible with life nor does it preclude a long life. In the literature 25 patients were children under twelve years of age. Eleven lived to be more than nineteen years old, and 3 patients reported were fifty-eight, sixty-five, and seventy-two years of age. This anomaly is more common on the left side.—*Agensis of the Lung*, A. R. Valle & E. A. Graham, *J. Thoracic Surg.*, August, 1944, 13: 345.—(W. M. G. Jones)

Resection of Vagus Nerve.—A case of a thirty-five year old soldier is reported in whom widening of the posterior superior mediastinum to the left of the midline was found on a routine chest film. The diagnosis of neurofibroma was suggested by the location of the tumor and by the physical examination which revealed numerous *café au lait* spots. The patient was asymptomatic. On opera-

tion, a pedunculated mass, 10 cm. in diameter, originating from the sympathetic nerve trunk was found in the posterior superior sulcus. There were two more tumors, 5 cm. in diameter, both originating from the left vagus nerve. All three tumors and a 15 cm. long portion of the left vagus nerve were removed. Histological section of the operative specimen confirmed the diagnosis of neurofibroma. The postoperative course was uneventful with the exception of a transient Horner's syndrome and paralysis of the left vocal cord.—*Resection of the Left Vagus Nerve for Multiple Intra-thoracic Neurofibromas*, B. Blades & D. J. Dugan, *J. A. M. A.*, October 16, 1943, 123: 409.—(H. Abeles)

Eosinophilic Pleuritis.—The true inflammatory nature of eosinophilic infiltrations has been amply proved on the basis of autopsy material. Pleural effusions accompanying these infiltrations are rare but some have been reported. Usually the effusion is not large enough to permit examination of a specimen. In a twenty-one year old soldier with a typical eosinophilic infiltrate of both lungs, bilateral pleural effusions developed. Diagnostic tap was performed, and in each instance amber clear fluid was obtained. On the right side the fluid contained 850 leucocytes with 29 per cent eosinophils. On the left side there were 2,600 white cells with 64 per cent eosinophils. The fluid was sterile on culture, including guinea pig examination for tubercle bacilli. Otherwise the disease ran a typical course with blood eosinophilia, eosinophils in the sputum, and with complete recovery. Thirteen weeks after onset of the illness many ova of ascaris were found in the stools, and in the following week two adult worms were passed following a vermifuge. After this the residual blood eosinophilia disappeared completely, although the cutaneous reaction for ascaris allergy remained strong. In the above case the causal connection between the ascaris infestation and the eosinophilic lung infiltrations is clear. Ascaris infestation is a common cause of this disease in Switzerland but undoubtedly other allergens are capable of

producing an identical pathological picture.—*Eosinophile Pleuritis bei flüchtigem, eosinophilen Lungeninfiltrat*, H. Baumann, Schweiz. med. Wchnschr., April 1, 1944, 74: 326.—(H. Marcus)

Chylothorax.—Many cases of chylothorax are not recognized. It should be suspected whenever a milky fluid is obtained at thoracentesis, especially if there is no obvious reason for the presence of pleural fluid. This milkiness is due to presence of excess fat and is pathognomonic of chylothorax. The fat may be recognized by the fact that it tends to rise as a creamy layer on standing; the fat stains readily by Sudan III; if the fluid is alkalized and shaken with ether the fluid clears; and chemical examination will show a fat content of 0.4 to 4.0 per cent. The lower values will be found in cases of hydrothorax which may occur in association with chylothorax. The usual bacteriologic and pathologic studies of pleural fluid are not of assistance in diagnosis. Chylous ascites and rarely chylopericardium may also occur in association with chylothorax. The etiology of chylothorax is varied: trauma, severe coughing, gunshot wounds, blast injuries, and over-vigorous attempts to resuscitate newborn infants. It may occur following thoracic duct injury in the course of surgical operations. In nontraumatic cases malignant disease is often responsible or tuberculosis. Filariasis may cause it. In the cases secondary to trauma there is usually a delay in onset, two to ten days, probably caused by its collection first in an extrapleural pocket, until rupture of the pleura takes place. Then dyspnea and shock are prominent symptoms. The accumulation of chyle may be massive and will require repeated thoracentesis. Dramatic relief is often experienced by this measure. Loss of large amounts of fluid produce dehydration and emaciation and even death in a few days. Development of peripheral edema in chronic cases is due to loss of serum proteins. In about 50 per cent of cases, healing of the ruptured duct takes place in several weeks. Spontaneous rupture

of the duct with similar features and mortality in children has also been reported. In non-traumatic cases, the clinical features are similar but it is insidious in onset. The prognosis is generally poor, especially in the nontraumatic forms, most frequently due to malignant disease. There is no satisfactory method of treatment. A high carbohydrate, high protein diet is advised. Aspirated chyle (using sodium citrate or heparin as anticoagulants) has been given intravenously but an occasional death has resulted. A safer method of restoring the blood osmotic pressure is to use blood plasma. Surgical closure of the ruptured ducts has not been successful. The introduction of sterile broth or gomenol into the pleural space to aid in the closure by production of an aseptic pleuritis has been reported. Diaphragmatic elevation by phrenic crushing cured one reported case. X-ray therapy of underlying malignant disease has benefited some cases.—*Chylothorax*, A. M. Olsen & G. T. Wilson, *J. Thoracic Surg.*, February, 1944, 13: 53.—(W. M. G. Jones)

Acute Empyema.—The treatment of pleural empyema is simple drainage; the drainage must remain adequate for as long as there is an abscess cavity. The time at which an empyema should be drained is a matter of clinical judgment. Aspiration should be performed frequently, slowly and without air replacement. When an empyema is ready for draining a liberal incision should be made, at least two inches of rib removed subperiosteally and a tube inserted. Pleural empyema has a bad reputation for healing, merely because of the lack of equal elasticity of the cavity wall. Here the resultant varying changes are due to movements of the intercostal muscles, the diaphragm and the chest wall. The author lists the following series of causes of inadequate drainage: (1) obstruction by fibrinous masses within the drainage tube; (2) obstruction by granulation tissue; (3) obstruction by kinking of tube; (4) tube too short to reach the pleura; (5) tube through the chest wall but not reaching the cavity;

(6) tube too far into cavity; (7) part of the cavity below the drainage opening; (8) loculation. When an empyema shows evidence of unsatisfactory progress the patient should be set upright in bed and the wound inspected. The tube should be removed. If a free flow of pus results then one realizes that the tube was too long. Never use force in probing a sinus because of the danger of air embolus, temporary paralysis or cerebral abscess. An uncomplicated acute empyema, kept properly drained and properly dressed, should pursue an uninterrupted course to recovery. If such steady progress is interrupted by a febrile attack, one is too often prone to use the sulphonamides and not investigate the tube and wound. The most likely cause of fever is inadequate drainage. The author stresses the importance of early physiotherapy to prevent contractures of the chest wall and interference with respiratory function. Breathing exercises and exercises for the major thoracic muscles are used. The author notes the large incidence of infected hemothorax due to improper treatment of the original condition. He states that blood and bloody fluid in the chest which result from trauma should be aspirated without air replacement. When infection is once established the chest should be opened, all clot evacuated and adequate drainage established. —*Management of Acute Pleural Empyema*, P. R. Allison, *Brit. M. J.*, September 25, 1948, 2: 388.—(D. H. Cohen)

Chronic Empyema.—The records of 346 patients with chronic empyema at the Mayo Clinic were studied to learn the cause of the chronicity and the methods used to eradicate it. Chronic empyema is not a disease but a complication of pneumonia, influenza, pleurisy, tuberculosis, trauma and acute exanthemata, in the order named. The most common causes of chronicity are (1) inadequate drainage, (2) tuberculosis, (3) too late drainage (that is, empyema not recognized early), (4) bronchial fistula and (5) bronchiectasis. There was no demonstrable correlation between clinical type of antecedent illness and

type of bacteria cultured from empyema cavity. It is safe to perform open drainage for pneumococcic pus if the specific gravity is 1,040. In streptococcic empyema the underlying lung infection must be combated first. Closed drainage or aspirations must be used until the specific gravity of the pus is 1,035–1,040. While most cases showed pleural thickening in X-ray films, in 6 per cent there was no visible pleural reaction. Prophylaxis of chronic empyema is the establishment of early, adequate drainage in every case of acute empyema. To be adequate, drainage must involve the removal of a portion of at least one rib. The more radical the drainage the shorter the patient's stay in the hospital and the lower the mortality rate. In cases with a thoracic sinus, pleural biopsy should be done to discover tuberculous infection, and a more radical drainage employed. The presence of bronchial fistula does not increase the mortality or morbidity rates, and many of them will heal spontaneously or with minor surgical attention. Closed drainage cured only 8 per cent but is of greater value as it keeps a cavity drained until the mediastinum becomes fixed and open drainage becomes safe. Seventy-one per cent of these cases had open drainage. Thoracoplasty was employed for only 5 per cent, as this is a very mutilating operation and should never be used unless absolutely necessary. The size of the cavity should be measured frequently (by filling the space with saline solution) and X-ray films taken also to record the progressive decrease in size of empyema. Irrigation of the space with Dakin's solution twice daily is recommended as an aid in lung expansion. If conservative treatment does not do this, more radical procedures (unroofing cavity or thoracoplasty) should be considered. In cases of mixed tuberculous empyema, thoracoplasty is particularly valuable and should be used early as lung fibrosis prevents lung reexpansion. Muscle transplants were used to fill spaces impossible to collapse by thoracoplasty (2 cases). A draining sinus may remain after almost total obliteration of the empyema cavity. Spontaneous healing of

sinus may occur but should be complete in a year. The causes of persistence of sinus are continuance of the chronic empyema, broncho-cutaneous fistula, tuberculosis, the presence of a foreign body, sclerosis of the walls of a sinus and osteomyelitis of a contiguous rib. In this series, 46 patients (out of the 212) had a draining sinus, but some of these were of short duration and may be healed by now. There were 18 deaths in the hospital and 3 deaths at home of causes related to the empyema. These deaths were from operative shock and spread of the infection by contiguity or metastasis, chiefly brain abscess. Of the 212 patients who answered a written inquiry, 164 stated their health was excellent and that they had resumed their usual mode of life.—*Chronic Empyema*, O. T. Chagett & V. D. Shepard, *J. Thoracic Surg.*, June, 1943, 12: 464.—(W. M. G. Jones)

Unusual Cause of Chronic Empyema.—The author lists the causes of chronic empyema as: inadequate drainage, foreign body, bronchopleural fistula, inexpandable lung, tuberculosis and fungus infections. He emphasizes another cause—dermoid tumors of the mediastinum, and presents 2 cases. The pleural involvement follows secondary infection within the lung. In both cases, tube drainage had been previously carried out for the empyema, and there were residual broncho-pleuro-cutaneous fistulae. Resection of the dermoid tumors resulted in cure in each case. Careful diagnostic study is stressed. Tubercle bacilli and fungi are sought in the sputum and sinus discharges by culture and guinea pig inoculation. X-ray films are taken in postero-anterior and lateral views with lipiodol injection of the sinuses. Dermoids are usually found in the anterior mediastinum, while the posterior costo-vertebral gutter is usually free of involvement. Fluoroscopy of stomach and colon are also suggested to rule out diaphragmatic hernia. Material from the sinus is examined for hair, etc. Because of malignant changes in at least 15 per cent of these tumors, early surgical removal is advised.—*Chronic Empyema Due*

to Dermoid Tumors of the Mediastinum, J. M. Dorsey, *Surgery*, May, 1943, 13: 755.—(D. J. Rednor)

Treatment of Empyema.—The main obstacle to the successful treatment of empyema by the closed method is the presence on the pleura of a thick layer of fibrinous, purulent exudate. Sodium tetradecyl sulfate is capable of liquefying this exudate, thereby paving the way for bacteriostatic agents. Among the latter, sodium sulfadiazine proved satisfactory, when used together with azochloramide which oxidizes the sulfonamide inhibiting peptones and para-aminobenzoic acid. The combination of azochloramide and a sulfonamide (sulfanilamide) had a definite bacteriostatic effect on *S. aureus* *in vitro*. *In vivo* the author uses 80 grains (5.2 g.) of sodium sulfadiazine in 100 to 200 cc. of azochloramide-tetradecyl solution, and leaves this mixture in the pleural cavity till the next irrigation. Physiological saline is employed as irrigating fluid. Sulfadiazine blood levels should be determined and the blood picture and the urine examined at frequent intervals. So far, no toxic signs were encountered. The case history of a thirty-six year old white female is given. Empyema (staphylococcal) developed in the course of pneumothorax treatment. After saline irrigations and penicillin therapy had failed to bring about improvement, azochloramide-tetradecyl-sulfadiazine treatment was instituted and continued weekly for three and one-half months. After five weeks the pleural fluid became clear and cultures turned negative. No relapse occurred up to date. Six other cases are under similar treatment.—*A Suggested Therapeutic Procedure for the Treatment of Empyema by the Closed Method: A Preliminary Report*, E. E. Carpenter, *Journal-Lancet*, August, 1944, 64: 278.—(P. Lowy)

Clotted Hemothorax.—Clotted hemothorax is a frequent complication of chest trauma. In a review of 426 cases of hemothorax, 10 per cent were clotted. The pathogenesis of the condition is not known. Infection is

said to favor clotting, but fully half of the operated cases were uninfected. Two types of hemothorax are seen. The more common clotted hemothorax is a multiloculated fibrino-hemothorax. The massive clot is less common. Physical signs are those of fluid or of consolidation in the latter type. The diagnosis depends on difficult or unsuccessful aspiration in a case which obviously has fluid in the pleural space. Small basal clots which produce no fever are left alone. Indications for thoracotomy are large clots, persistent temperature elevation, multiloculated fibrino-hemothorax and clotted hemothorax with foreign body. When the entire lung is collapsed, no time is lost in operating. When the upper lobe is expanded, the formation of adhesions to the upper lobe is awaited before thoracotomy. The optimum time is somewhere between three and five weeks following injury, but cases from two weeks to two months have been operated on. After a time interval longer than two months reexpansion of the lung cannot be expected. The pleural space is approached through an intercostal incision. A section of the sixth rib is sometimes resected for better exposure. The clot is evacuated and the dense fibrin coat overlying the visceral pleura is removed. If this is not done lung expansion is slow or incomplete. The fibrin layer is incised, and it can usually be lifted away from the visceral pleura by finding the plane of cleavage with the finger. Oozing from the visceral pleura is rarely severe. It is severe, however, from the parietal pleura, and the fibrin there is not removed other than from the costophrenic sinus and part of the diaphragm. Sodium penicillin is instilled following the operation, and the drain which is placed into the wound is not opened until twelve hours postoperatively. In uninfected cases it can usually be removed on the fifth day, when the discharge is less than one ounce. The results are best in uninfected cases, and there were no fatalities in this group. Even the empyema group does remarkably well, and only one case died of *Staphylococcus aureus* septicemia several weeks postoperatively.—*Clotted Hemothorax*, R. W.

Lush & J. C. Nicholson, Lancet, October 7, 1944, 247: 467.—(H. Marcus)

Intrathoracic Foreign Bodies.—At a Forward General Hospital, 30 per cent of all severe chest casualties had retained foreign bodies. Out of 92 cases seen with foreign bodies, 50 were operated on, and the foreign body was removed in 49 instances. Removal of the foreign body is always advised if it is more than one cm. in diameter, or if it is of a jagged appearance. There were 2 deaths following the operation, one in which the missile was embedded in the heart and could not be recovered following pericardiectomy, and one in which the missile was in the right upper lobe where it had caused abscess formation and septic erosion of the ascending aorta. The best time for operation is the earliest moment at which the patient's condition permits. Ten days after wounding is the average, unless the foreign body is pleural and an obvious empyema is present. Then the foreign body is removed at the time the empyema is drained. Accurate X-ray localization is of prime importance. Intrapulmonary or mediastinal foreign bodies are best demonstrated by anteroposterior and lateral films. If the missile is near the chest wall, fluoroscopic examination is necessary to decide whether the missile is intrathoracic or extrathoracic. Thoracotomy with rib resection provides the usual approach. The exact site depends on the location of the foreign body. For small intrapleural or superficial intrapulmonary foreign bodies, intercostal incision may suffice. When there is no gross evidence of infection the chest is closed without drainage. Penicillin is used in infected cases, and in cases who develop infected effusions later on. Such effusions are handled by needle aspirations. Thorough removal of blood clot and fibrin from the pleural space at the time of operation is indicated.—*Intrathoracic Metallic Foreign Bodies*, A. L. D'Abreu, J. W. Litchfield & C. J. Hodson, *Lancet*, August 26, 1944, 247: 265.—(H. Marcus)

Wounds of Chest.—Chest injuries are divided, for clinical purposes, into nonpene-

trating wounds and penetrating wounds. The nonpenetrating wounds include contusions and open wounds which do not penetrate the parietal pleura. The superficial open wounds should not be treated by complete excision since the relationship of the soft tissue layers may be markedly different at the time of treatment from the one at the time the injury was sustained. Penetrating wounds when of minimal extent and without complications are best treated by immobilization with adhesive strapping and morphine to assure rest. The patient is kept in bed in Fowler's position for several days. Large wounds of the thoracic wall may produce a serious picture caused by paradoxical respiration. In addition, the mediastinal flutter may cause twisting of the mediastinal structures inducing circulatory embarrassment and reflexes on the vasomotor system resulting in shock. Treatment consists in immediate closure of the wound by anything at hand followed by the usual measures to combat shock. After the shock has been overcome attention is being paid to further treatment of the chest wound. Under field block anesthesia or, if necessary, under inhalation anesthesia, preferably with cyclopropane, the wound is excised, bleeding controlled, the visceral pleura closely inspected for tears, sulfanilamide instilled into the pleural cavity and the wound is closed with stay sutures. If there was obvious contamination of the pleural cavity closed drainage may be established. Following closure of the wound the lung is expanded by aspiration of air and by using positive pressure. Another serious injury results when a valve-like mechanism is produced by the wound. Marked respiratory embarrassment is caused by the resulting tension pneumothorax. Circulatory distress is less prominent in this type of chest injury. Treatment consists of under-water decompression by needle or catheter; the latter is preferable if there is a simultaneous hemothorax or lung injury. If the chest injury is complicated by an internal hemorrhage, usually from an intercostal vessel or from an

internal mammary vessel, conservative treatment is to be preferred. If respiratory embarrassment is produced the hemothorax should be gradually decompressed with simultaneous air replacement in order to keep up the pressure tamponade. Not more than 500 cc. of blood should be removed at one time. Many serious chest injuries are complicated by injuries of the lung. Tension pneumothorax or hemopneumothorax are the most common complications. When the pulmonary damage produces shock which does not respond to the usual therapeutic measures, radical procedures have to be employed since it was demonstrated by operative and autopsy findings that there is usually gross interstitial pulmonary hemorrhage present. Another indication for surgical intervention is damage to the great pulmonary vessels. The nature of the surgical procedure may vary from ligation of a vessel to pneumonectomy depending upon the findings in the individual case. If a communication of the abdominal cavity with the pleural cavity is produced by the injury the abdomen should be explored first and then a thoracotomy with catheter drainage should be performed. Injuries to the intrapericardial structures may produce cardiac tamponade manifested by the Beck triad, a falling arterial pressure, a rising venous pressure and a quiet heart; paradoxical pulse, distention of veins of the neck and reduction of cardiac excursions on fluoroscopic examination may also be present. Cardiac tamponade will not develop when the blood can enter the pleural or abdominal cavity through the opening in the pericardium but severe hemorrhagic shock will dominate the clinical picture. In these cases the clinician may suspect a cardiac injury by the position of the wound of entrance and the profound degree of shock. Treatment consists in closure of the heart wound and evacuation of the pericardial contents. The death rate from wounds of the heart is about 23 per cent.—*Wounds of the Chest, E. J. McGrath, J. A. M. A., February 19, 1944, 124: 488.*—(H. Abeles)

Thoracic Injuries.—Thomas describes the nature and treatment of thoracic injuries in the forward area of war zones where operative facilities are not the elaborate ones found in relatively stationary areas. The more serious thoracic injuries often prove fatal before there is any possibility of removal to an operating unit. The cause of death of these cases, apart from shock and hemorrhage, is severe interference with the cardio-respiratory mechanism which continues to operate as a cause of death during the first forty-eight hours after receipt of the injury. If the patient survives this period, the cause of death is generally a direct result of superimposed infection. Shock is a variable factor in chest injuries and is usually in proportion to the degree of tissue damage. In many cases the simple anti-shock remedies of warmth, both externally and internally, of hot drinks with morphia to control pain will be enough. Oxygen therapy is a valuable measure, particularly if there is any respiratory embarrassment. The absence of shock is no indication for allowing the patient freedom of movement. The chief function of the forward unit is to relieve immediate symptoms caused by cardio-respiratory embarrassment and secondarily to institute treatment which will decrease the incidence of complications. The commonest causes of interference with normal cardio-respiratory function are: (1) open pneumothorax, (2) tension pneumothorax and (3) much more rarely tamponade of the heart by blood in the pericardium. These three conditions will demand adequate treatment. Surgical emphysema, a common occurrence, is usually of limited extent and has little clinical importance. The severe type is most often the result of an underlying tension pneumothorax. Stove-in chest may constitute a serious threat to the patient from the paradoxical movement of the chest wall. It may result from crush injuries and is commonly associated with a hemothorax and acute dilatation of the stomach. The commonest condition met which does not menace life in the early course is hemo- or hemopneumothorax

with or without a retained foreign body. Under ideal conditions, the object of treatment should be the removal of every medium of infection, that is, foreign bodies of all kinds, removal of all damaged tissue and rapid re-expansion of the lung. In a forward area, however, this is not possible so that a certain percentage of cases develop late infection which require later more extended treatment in a thoracic centre. Conservative treatment of hemothorax involves aspiration without gas replacement. The author gives pertinent reasons why gas replacement is contraindicated. Concerning the use of sulfonamides, the author deprecates the tendency to depend too much on chemotherapeutic aids at the expense of violating basic surgical principles. —*Thoracic Injuries: The Role of the General Surgeon in the Forward Area*, C. P. Thomas, *Brit. J. Tuberc.*, July-October, 1943, 37: 103.—(E. H. Rubin)

Chest Wounds.—The author records his experience at a casualty clearing station in the immediate treatment of thoracic casualties. The aim was to ensure that the patient had recovered sufficiently to withstand the rigors of evacuation to a chest centre. The material consists of 127 consecutive battle casualties with penetrating wounds of the chest. The majority had passed through a surgical unit, but treatment had been confined to dressing and the administration of morphine. Those admitted within forty-eight hours of wounding comprised 46 per cent of the cases; those within seventy-two hours 72 per cent. An analysis of the intrathoracic status revealed that 88 (69.4 per cent) had haemothorax and/or hemopneumothorax—5 of these were fatal; 13 (10.2 per cent) had thoraco-abdominal injuries—6 of these died; 14 (11.0 per cent) had pulmonary hematoma; 5 (3.9 per cent) each fell in the groups of pneumothorax and atelectasis and there were 2 cases of lung abscess. In hemothorax the bleeding is seldom of long duration and is checked by pulmonary collapse. The presence of blood in the pleural cavity provokes a

serous reaction. In case of hemopneumothorax the air may enter the pleural space from within or from without. Only one case of tension pneumothorax was noted. Infection was the earliest complication occurring in 9 of the 88 cases. In each case the infection was caused by the *Str. hemolyticus*, and was established within seven days of wounding. The ideal treatment in traumatic hemothorax is to empty the pleural space—with or without air replacement depending on symptoms. Repeated aspirations were done in the cases of infective hemothorax, but in 5 cases closed drainage was necessary. The patients received 4 g. of sulphanilamide daily for six days. Of these 88 cases, 5 were fatal before evacuation; none died subsequently. Atelectasis was noted in 5 cases and was probably a sequel of bronchial obstruction by aspirated blood or secretion. Treatment of these 5 cases was confined to attempts to moderate the pain and to promote drainage by posture; infection was discouraged by sulphapyridine. In all 5 cases uneventful re-aeration was achieved. The author's experience leads him to conclude that the immediate treatment of the parietal wound should be as conservative as possible. The indications are to control hemorrhage from the chest wall and to close an open pneumothorax. If there is no serious hemorrhage and the wound is not "sucking," simple dressing is adequate; if the wound is "sucking" it should be closed by strapping over an air-tight pad and the intrapleural pressure lowered by aspiration of the hemothorax.—*The Early Treatment of Wounds of the Chest in the Middle East*, R. B. Scott, *Brit. M. J.*, April 8, 1944, 1: 490.—(D. H. Cohen)

Closure of Open Chest Wounds.—A muscle plastic operation is described for the closure of the wide open chest following the Schede operation. The accepted treatment for tuberculous empyema is radical surgery: thoracotomy, thoracoplasty and Schede operations. The anatomical result is a wide open chest with exposed lung, taking months and years to close if spontaneous closure takes

place at all. A muscle plastic closure cannot be satisfactorily accomplished at the time of the Schede operation. The reasons are: the toxemic condition of the patient with an empyema cavity and the failure of muscle flaps to adhere in the presence of severe infection, especially if the tubercle bacillus is a causative factor. The operation should be planned far in advance so that at the time of the thoracoplasty and Schede procedures, a minimum amount of extracostal musculature will be traumatized or sacrificed. Small residual empyema cavities may be closed by resecting the scapula and implanting a pedicled flap of scapular and latissimus dorsi muscles. Larger chest defects require, in addition, a graft of erector spinae muscle to cover the exposed lung. Postoperative wounds heal by primary union as early as four to six weeks. On the other hand, if left to close spontaneously, patients with open chest wounds remain in the hospital as long as three years. Six patients have been operated upon according to this technique, with success in 5 cases and failure in one. All 5 patients are well enough to earn a livelihood in part at least, and one patient went through childbirth without incident. The unsuccessful result occurred in an emaciated individual, weighing about 75 pounds, who had an unrecognized caseous focus in his lung at the time of operation. The result was extensive tuberculous infection in the wound and a hematogenous dissemination throughout the body. The principles involved in this operation have been successfully used by the author in treating patients with chest defects resulting from nontuberculous empyema. The absence of tuberculous inflammation in such cases makes for less chance of complications and more rapid wound healing. (Author's Summary.)—*Closure of Open Chest following the Schede Operation for Tuberculous Empyema*, M. Weinstein, *Surg., Gynec. & Obst.*, August, 1944, 79: 148.—(G. C. Leiner)

Penetrating Chest Wounds.—In a general hospital, located midway between the forward base hospital and the chest centre in England—

the mortality from chest wounds and their complications is relatively low. Patients whose condition is good enough to be removed from the forward hospital to a general hospital have a good chance to survive. In a series of 260 cases, 15 deaths were recorded. Empyema was by far the most common serious complication; it was the contributing cause of death in 13 of the fatal cases. Hemothorax was the most frequent mild complication; it was present 125 times. It is treated by prompt aspiration which is repeated if necessary. Small amounts of air are injected only if the patient's comfort demands it or if the X-ray localization of pockets is to be facilitated. If clotting of the blood occurs in the chest, the clots are usually left undisturbed. Complete reexpansion of the lung is the rule. However, clotting in a hemothorax frequently foreshadows infection which has to be treated vigorously. Pyothorax was the most common serious complication. It was present 77 times. It is treated by repeated needle aspiration and instillation of sodium penicillin. If the infecting organisms are gram positive cocci or clostridia, the results of penicillin treatment are very good. In loculated empyemata needle aspirations are insufficient and rib resection and "nettoyage" are done. Adhesions between pockets are broken at operation and large pieces of fibrin are removed from the pleural cavity. Intrapleural and intrapulmonary foreign bodies are removed at the same time. After operation, underwater drainage through a tube is provided. With adequate drainage, lung expansion is the rule, even in cases with bronchopleural fistula. Drainage must be continued not only until discharge ceases, but until it can be demonstrated by the injection of contrast medium that the empyema cavity has become obliterated. Atelectasis of one or more lobes occurred 44 times. Reexpansion is the usual outcome of this complication. Extrapleural hemothorax was found 15 times and was treated by aspiration. All foreign bodies, whether intrapleural or intrapulmonary, were removed if they were over 1 cm. in diameter, provided that the patient's

condition permitted. Thoraco-abdominal wounds were present 34 times. Two of these patients died. Treatment of these wounds must include suture of hollow viscera through an abdominal, a thoracic or a combined approach. Subphrenic abscess was a complication 7 times, and all patients recovered following drainage of the abscess. When the diaphragm is injured it is sutured at the time the empyema is drained. Penicillin has also proved of great value in infected wounds of the chest wall where it is used locally in the form of calcium penicillin. It can be administered through Carrel-Dakin tubes which have been sewed into place. When pyopneumothorax is associated with infected chest wounds penicillin is also given parenterally. In the treatment of empyema, however, parenteral administration is useless because the thick pleura acts as a barrier.—*Major Complications of Penetrating Wounds of the Chest*, J. W. Litchfield & C. J. Hodson, *Lancet*, August 12, 1944, 247: 197.—(H. Marcus)

Pectus Excavatum.—The author presents the only 2 entirely successful cases operated on at the Massachusetts General Hospital. The operation was according to the principles put forth by Dr. A. Lincoln Brown. The patients were two sisters, fourteen and five, the elder suffering from dyspnea, the younger symptomless. In both, the deformity was steadily becoming more prominent. The operation consists primarily of removing appreciable lengths of the lower costal cartilages and a wedge of bone at the upper limits of the gladiolus. A vertical midline incision is used, the xiphoid process removed and the rectus muscles reflected from their attachments. The diaphragmatic attachments are then cut and the costal cartilages divided up to the second or third rib. A transverse wedge of bone is then removed from the sternum just below the articulations of the second or third costal cartilages. Wire sutures are used to hold the trimmed lower portion of the sternum up in the proper position. Large segments of costal cartilage are

then removed and held in place by heavy silk sutures. In closing the skin, the redundant portion is removed. At the end of the operation a light breast plate of plaster was moulded to fit the anterior chest wall to prevent paradoxical motion. No external traction was employed.—*Pectus Excavatum: Report of Two Cases Successfully Operated On, R. H. Sweet, Ann. Surg., June, 1944, 119: 922.*—(D. J. Rednor)

Anesthesia in Bronchoscopy.—To obviate the unpleasantness of the bronchoscopic procedure for the patient, intravenous pentothal anesthesia has been advocated. The patient is given premedication of morphine and scopolamine or atropine. Eight cc. of a 5 per cent pentothal solution are injected over a thirty-second period. To avoid the danger of laryngeal spasm and cessation of respiration, 10 per cent carbon dioxide and oxygen are given through a tube, and the anesthetic is injected only when the patient's respiration becomes hyperpneic. The larynx is exposed with the laryngoscope as soon as the patient's jaw muscles relax, and when the glottis is open the bronchoscope is introduced immediately. Otherwise this event is awaited. During the procedure, 10 per cent carbon dioxide in oxygen may be administered continuously through a tube hooked into the corner of the mouth. This gas mixture is administered again through the side tube of the bronchoscope just before the instrument is withdrawn through the larynx. With this procedure, withdrawal spasm is usually avoided, but if necessary the gas mixture can be given through a positive pressure mask after the bronchoscopy. The advantages of the procedure are mainly those of the comfort of the patient, especially in case of repeated bronchoscopic treatments. The disadvantages and contraindications are those of pentothal anesthesia in general. It is inadvisable in cases presenting respiratory difficulties, an additional cocainization may be necessary in patients who present technical difficulties due to configuration of mouth, jaw and neck.—*Pentothal Anaesthesia in Bronchoscopy, L.*

Fatti & H. J. V. Morton, Lancet, May 6, 1944, 246: 597.—(H. Marcus)

Spontaneous Diaphragmatic Paralysis.—Spontaneous paralysis of the phrenic nerve, particularly in children, is not a very common occurrence. In the case reported, X-ray films revealed paralysis of the left half of the diaphragm in a nine year old child. In addition, there were enlarged hilar lymph nodes on the left and a thickened interlobar fissure, suggestive of a residual interlobar effusion. It is thought that the paralysis was caused by compression either by the lymph nodes, the pleural effusion or both. Anatomical conditions are such that a paralysis of the phrenic nerve may occur more readily on the right than on the left. The commonly expressed opinion that spontaneous paralysis may be caused by enlarged lymph nodes alone, however, does not satisfy the author, because in that case the vagus too should be involved by the compression. Paralysis of the vagus, however, is an extremely rare condition. The author concludes that in the case reported there was an abnormality in the anatomical course of the left phrenic nerve which made it possible for the enlarged lymph nodes to compress the nerve.—*Su un caso di paralisi spontanea dell'emidiaframma sinistro in un bambino, A. Traversa, Riv. di fisiol., 1940, 13: 206.*—(G. Simmons)

Pneumopericardium.—A forty-two-day-old Negro infant was readmitted to the hospital thirty-two days after birth because of abscess of the right buttock. The baby had had a healthy father, but her young mother had had a positive Wassermann during pregnancy and had undergone antiluetic therapy consisting of a series of bismuth and neoarsphenamine injections. Delivery was difficult due to the large size of the infant. White asphyxia was present, requiring artificial respiration and the use of respiratory stimulants. Vitamin K and 20 cc. of blood had been given into the right buttock. The immediate postnatal hospital course was eleven days due to some transitory neurological abnormalities. The

abscess of the right buttock was incised after readmission, but it failed to heal. Instead it progressed to rectal fistula formation. There then occurred an episode of acute dyspnea accompanied by bubbling râles and distant heart sounds. The febrile course was unaltered by sulfapyridine therapy, so a chest X-ray film was taken. This revealed pneumopericardium, disseminated bronchopneumonia and two large abscesses in the right lower lobe. Following a second attack of dyspnea, the child died. Autopsy confirmed the X-ray findings, gas escaping under tension when the parietal pericardium was incised. The larger of the two abscesses was in intimate contact with the pericardium and was also in communication with a fairly large bronchus. Staphylococci were recovered from the lung abscess.—*Pneumopericardium in a Forty-two Day Old Infant, Am. J. Dis. Child., April, 1944, 67: 288.*—(K. R. Boucot)

Dilatation of Pulmonary Artery.—Congenital dilatation of the pulmonary artery is rare. Recognition of this condition rarely occurs before necropsy. Radiology plays an important part in the diagnosis of this condition, and the criteria of X-ray diagnosis seem to be as follows: (1) increase of pulmonary bow; (2) small aortic knuckle; (3) broadening of hilar shadows; (4) enlargement of the pulmonary arterial tree. The authors give a clinical history of a patient believed to have the above named condition. He is a man of twenty-three who was admitted for influenza, but routine examination revealed certain peculiar features. He was 6 ft. 5½ in. in height and had clubbed fingers and a blue tinge on his lips. He had been told in childhood that he had "heart trouble." He had no illnesses and lost no time from schooling. Three years before admission he had a bout of blood spitting which was not repeated. He gives no history of rheumatic fever. Examination of the heart reveals the apex beat to be well out. There was a palpable diastolic thrill over the precordium. On auscultation there was a mid-diastolic murmur at the apex. The lungs were clear. Blood

pressure 140/70; RBC 7.5 million; Hb over 140 per cent (Sahli). The electrocardiogram revealed diaphasic QRS complexes. X-ray examination demonstrated a huge pulmonary artery with a comma-shaped branch, also greatly enlarged in the antero-posterior position. After a barium swallow a very large impression made by the right pulmonary artery in the right oblique position was a striking feature.—*A Case of Congenital Dilatation of the Pulmonary Artery, H. L. Heimann & M. M. Posel, Brit. M. J., October 23, 1943, 2: 512.*—(D. H. Cohen)

Lupus Erythematoses Familialis.—Familial lupus erythematoses is very rare. Twenty-one cases of lupus erythematoses occurring in 2 or 3 members of a family have been reported; 17 times the occurrence in brothers and sisters has been seen, only 4 times in parents and children. This report concerns 3 sisters, forty-five, forty-eight and fifty-four years of age, with the same localizations (nose, jaws) and with the same clinical form of the disease (discoïd). Improvement took place in all 3 of them after almost the same treatment.—*Lupus Erythematoses Familialis, A. D. Jaworowska, Urol. & Cutan. Rev., July, 1944, 48: 333.*—(G. C. Leiner)

Chronic Myeloid Leukemia.—A case is reported of chronic myeloid leukemia which was diagnosed in November, 1935, and was followed in Lakeside Hospital Out-Patient Department between eight periods of hospitalization. The patient was treated intermittently with Fowler's solution and on three occasions received roentgen ray therapy. There was a good response to both types of treatment. Five months prior to death pleurisy developed on the left following a head cold, and X-ray examination revealed a pleural effusion. Serial X-ray films revealed an increase in the pleural effusion and, subsequently, parenchymal infiltration. The pleural fluid was positive for tubercle bacilli. During the final four weeks of illness the patient received nine to twelve minims of Fowler's solution daily. No X-ray therapy

had been given during the preceding eight months. On the day of death the white blood count was 12,850 per cc.; the differential count, 82 per cent polynuclears, 9 per cent myelocytes, 2 per cent myeloblasts, 5 per cent basophils, one per cent lymphocytes and one per cent monocytes. Autopsy revealed miliary tuberculosis of the lungs, liver, spleen, kidneys, bone marrow, lymph nodes and adrenal glands; active primary tuberculosis of upper left lung and hilar lymph nodes; myeloid metaplasia of bone marrow; splenomegaly, hepatomegaly and chronic adhesive fibrous pleurisy. Bone marrow sections from sternum, vertebra and long bones showed only myeloid hyperplasia and metaplasia. There were increased numbers of myeloid elements without a marked increase in immature forms, and all the marrow contained adequate numbers of red blood elements and megacaryocytes. Leukemic infiltration in other organs was completely absent even in the spleen. It is impossible to say whether these findings were due to the drug or the infection, but it is felt that the infection probably played an important part and may have produced some factor during the course of the leukemia causing the reticulo-endothelial system to revert towards normal. If the mechanism of this process were known, the pathogenesis of leukemia might be more readily discernible.—*Morphologic Obliteration of Chronic Myeloid Leukemia by Active Tuberculosis*, R. W. Heinle & D. R. Weir, *Am. J. M. Sc.*, April, 1944, 207: 450.—(G. F. Mitchell)

Regional Enteritis.—This disease of unknown etiology is recognized as a clinical and pathological entity by characteristic gross and

microscopic changes of the involved bowel. The lesion starts as an acute inflammation in the intestinal mucosa, proceeds to ulceration and, in the chronic stages, to stenosis and fistula formation. Patchiness of involvement is characteristic. Healthy bowel alternates with severely diseased segments, and it is common to find lesions of various ages in one segment, so that all phases of the disease may at times be observed in one specimen. When the mucosa is involved, it presents shallow ulcers with a vascular granulation tissue as their base. The villi are often hypertrophic. The submucosa is edematous and infiltrated with a cell-rich exudate. The muscularis mucosae shows relatively few changes. A neuromuscular hyperplasia of its component elements is commonly seen, and the same reaction is encountered in the outer muscular coats. It is unclear whether the hyperplasia of the nervous elements of Auerbach's plexus is only apparent due to contraction of involved segments or whether it is real. The serosa shows striking changes in and around the lymphatic channels, amounting frequently to occlusion of the latter. Miliary serosal nodules with epithelioid cells and giant cells are fairly characteristic, and these often lead to a mistaken diagnosis of tuberculous enteritis. Tubercle bacilli have never been demonstrated in these lesions. Cellular infiltration along the lymphatic channels of the mesentery and hyperplasia of the nodes draining the affected bowel are common. The involvement of the lymphatic systems suggests that obstruction of the lymphatic drainage may play a rôle in the etiology of the disease.—*Regional Enteritis*, F. Owens, *Arch. Surg.*, June, 1944, 48: 472.—(H. Marcus)

TUBERCULOSIS IN HOUSEHOLD ASSOCIATES¹

The Influence of Age and Relationship

RUTH R. PUFFER, H. C. STEWART AND R. S. GASS

The chief purpose of the epidemiological study of tuberculosis is to learn the selectivity exhibited by the disease. Distinction must be made between tuberculous infection, which is an almost inevitable sequel to exposure to tubercle bacilli, and tuberculous disease, which is highly selective. We need the answer to the important question: Why do only certain persons, constituting a relatively small proportion of those infected, develop tuberculosis? A factor in addition to exposure to tubercle bacilli or a combination of factors is necessary to set in motion the chain of symptoms and pathological processes which constitute one or another of the clinical types of tuberculosis. Possible factors are unusual dosage of bacilli (excessive exposure), age at first and subsequent exposure, and incapacity of the body to repel the invasion (susceptibility).

In epidemiology, rates of prevalence, incidence and mortality are useful for the comparison of the experience in different groups of the population. These rates may be obtained for persons differing according to household exposure to tubercle bacilli, that is, for household associates of sputum-positive and sputum-negative tuberculosis patients. In comparing these rates, the assumption is made that the differences are attributable to the known variable, that is, variation in exposure to tuberculosis. Although intimacy of contact between a patient and his associates may vary considerably, the opportunities for infection are more nearly equal for household associates of sputum-positive tuberculosis patients than for any other groups available for study. The members of this group, however, are not necessarily equivalent regarding other factors. Further subdivision of the group of associates is essential to understand the significance of such factors as susceptibility to the disease as well as the effects of exposure to tubercle bacilli.

In previous papers (1, 2, 3) it has been shown that the risk of developing tuberculosis for persons living in household association with a tuberculosis patient known to be sputum-positive is great. Also, the risk is greater for associates of open cases than for associates of cases not known to be sputum-positive. Attack rates are high for associates exposed to tubercle bacilli in the home; nevertheless, many of those exposed never develop the disease.

The present paper reports the prevalence of manifest tuberculosis at the time of investigation and the attack rates during observation according to exposure to tubercle bacilli, age, and relationship of the associates to the person with tuberculosis directing attention to the family. An additional factor, which was not considered in previous papers—relationship by blood to the tuberculosis

¹ From the Tennessee Department of Public Health, Nashville, Tennessee. This investigation was made possible by the financial support of the International Health Division of Rockefeller Foundation.

patient—is evaluated. For correct interpretation of this material, rates by age group are essential and are presented.

During the period from December 12, 1931 to January 1, 1941, 519 white and, 111 colored persons with tuberculosis directed attention to their families.² These persons are termed "index cases" in the Williamson County Tuberculosis Study (1). On discovery of the index case an investigation of the family was made and all members were urged to have an examination in the clinic. Through history, examinations and observation, nearly all cases of manifest tuberculosis are believed to have been discovered in these household associates.

COMPOSITION OF FAMILIES

The composition of families varies according to the age of the person directing attention to the family. If the person with tuberculosis is a young married person, the family group usually includes a consort and young children. If the

TABLE 1
Relationship of white and colored household associates to the index cases

RELATIONSHIP	WHITE		COLORED	
	Number	Per cent	Number	Per cent
Total.....	2,029	100.0	517	100.0
Parent.....	119	5.9	68	13.2
Sibling.....	177	8.7	102	19.7
Child.....	906	44.7	139	26.9
Consort.....	360	17.7	44	8.5
Other.....	242	11.9	95	18.4
None.....	225	11.1	69	13.3

person with tuberculosis is young and unmarried, the group includes siblings and parents. If the person is in an older age group, the married children have probably established homes of their own and the family group may be small. In all types of families, the household associates may include other persons related by blood and also some not related, as those related by marriage to some member of the family. The relationship of the associates to the index cases in white and colored families is given in table 1.

Since the persons termed index cases in white families were, on the average, older than similar persons in colored families, the relationship of household associates differed for white and colored families. While 906, or 44.7 per cent, of the 2,029 household associates in white families were children, in colored families

² In previous publications (1, 2, 3) this material was presented for the two groups of index-cases (a) cases of tuberculosis classed sputum-positive and (b) cases of tuberculosis not known to have positive sputum. When a case changed from sputum-negative to sputum-positive it was added to the sputum-positive group. Since in this report it is desirable to discuss the entire group of associates without duplication, the original classification of the index case is used in the presentation of data regarding prevalence.

only 139, or 26.9 per cent, were children. The proportion of siblings was greater in colored families (19.7 per cent) than in white families (8.7 per cent). The number of colored consorts, marital partners of index cases, was small, 44. There were 360 consorts in the white families. These differences are principally due to the age of the person drawing attention to the family.

A relatively small number of persons, 225 in white families and 69 in colored families, were not related by blood or marriage to the person with tuberculosis, the index case. Those who were related and were classed "other" include grandchildren, nephews and nieces, aunts and uncles, etc.

In this investigation of the prevalence of tuberculosis according to relationship, it is necessary to consider age of the associates. Children in the families are usually young; consorts are older; and parents are, on the average, the oldest of these groups being studied. Therefore, the data are viewed by age groups in order to determine the nature of the differences.

PREVALENCE OF MANIFEST TUBERCULOSIS IN WHITE AND COLORED FAMILIES ACCORDING TO THE AGE GROUP

In a previous report (2), a comparison of the prevalence of tuberculosis in white and colored families was presented in relation to the character of the index case. The prevalence of manifest tuberculosis among associates of sputum-positive cases was found to be no greater at the time of investigation in colored than in white families. The prevalence of tuberculosis at any given time is the product of two factors, namely: (1) the incidence of the disease, that is, the number of new cases developing in the population, and (2) the duration of the case with tuberculosis, the period from onset to death of the patient. The course of the disease is more rapid in colored than in white persons. The duration of the disease in colored persons is usually relatively short. Many white persons, however, are found to have a limited tuberculous process which often becomes arrested, and thus cases of tuberculosis accumulate in the white population. In the colored population many of the cases are eliminated rapidly from the population by death; in the white population a smaller proportion terminate in death from the disease.

This accumulation of cases in the white population is reflected in the prevalence of manifest tuberculosis by age groups (table 2). In the oldest age group under study, 56 of the 600 household associates were found to have manifest tuberculosis. The percentage, 9.3, is unusually high. In the young adult age group, 15 to 34 years, only 2.0 per cent had manifest tuberculosis at the time of investigation of the family. In children under 15 years of age, manifest tuberculosis was rarely found, with but 3 of the 794 children with manifest tuberculosis on investigation. This great variation in the prevalence of tuberculosis in white associates necessitates consideration of age in the study of other factors.

In the colored household associates there was only a slight variation in the prevalence of manifest tuberculosis by age groups. In all three age groups considered, manifest tuberculosis was found rather frequently. The 7 children with manifest disease were twins at 2 months of age, one each at 9, 10 and 13

TABLE 2

Prevalence of manifest tuberculosis at the time of investigation in white and colored household associates according to character of index case by age group

AGE GROUP	TOTAL			INDEX CASE SPUTUM-POSITIVE			INDEX CASE OTHER THAN SPUTUM-POSITIVE		
	Total	Manifest Tuberculosis		Total	Manifest tuberculosis		Total	Manifest tuberculosis	
		Number	Per cent		Number	Per cent		Number	Per cent
White									
Total.....	2,029	72	3.5	452	36	8.0	1,577	36	2.3
Under 15 years.....	794	3	0.4	154	3	1.9	640	0	—
15-34 years.....	635	13	2.0	138	5	3.6	497	8	1.6
35 years and over.....	600	56	9.3	160	28	17.5	440	28	6.4
Colored									
Total.....	517	21	4.1	326	19	5.8	191	2	1.0
Under 15 years.....	215	7	3.3	147	7	4.8	68	0	—
15-34 years.....	166	6	3.6	94	5	5.3	72	1	1.4
35 years and over.....	136	8	5.9	85	7	8.2	51	1	2.0



SPUTUM-POSITIVE INDEX CASE



OTHER THAN SPUTUM-POSITIVE INDEX CASE

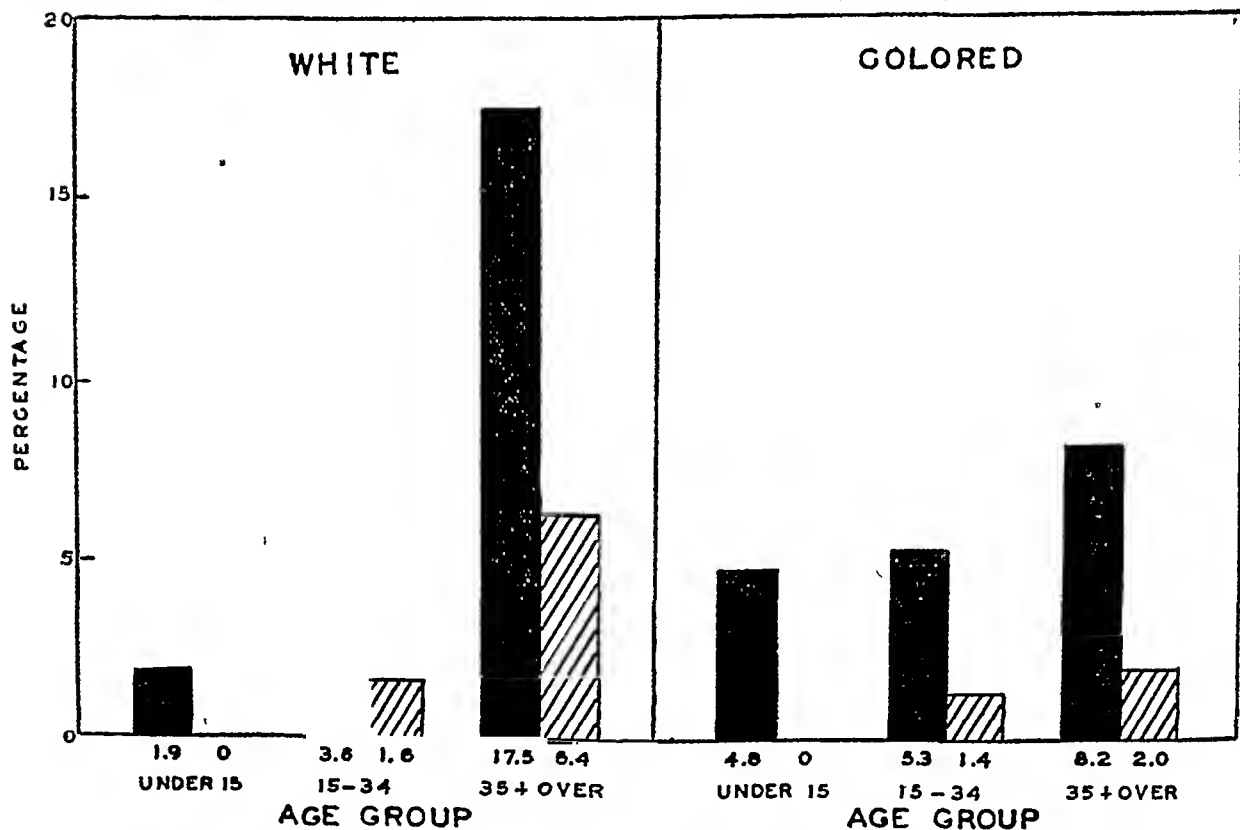


CHART 1. Percentage of white and colored household associates found to have manifest tuberculosis at the time of investigation according to character of index case by age group.

years, and 2 at 14 years of age. Even if there is a period in childhood when children have some immunity to tuberculosis, these figures suggest that the period is short. Examination of colored household associates in all three age groups seems to be productive.

Data are also given in table 2 to show the prevalence of manifest tuberculosis according to known household exposure. These percentages for white and colored household associates are shown in chart 1. In all three age groups manifest tuberculosis was found more frequently in persons exposed to open cases of the disease than in those exposed to cases not known to be sputum-positive. Both factors, age and household exposure to tubercle bacilli, are important variables.

PREVALENCE OF MANIFEST TUBERCULOSIS ACCORDING TO RELATIONSHIP

In the comparison of prevalence of tuberculosis according to relationship to the index case, difference in the ages of children, siblings, parents, etc. causes difficulties. Since no persons appear in certain age groups (for example no parents nor consorts under 15 years of age) an adjustment for age is unsatisfactory. It will, therefore, be necessary to compare the prevalence of tuberculosis according to relationship by age group. The findings in white families will be considered first.

White household associates under 15 years of age consisted principally of children of the person directing attention to the family. Nearly two-thirds (525) of the associates were children. Of these 525 children, 3 were found to have manifest tuberculosis on investigation of the family. No other cases of persons under 15 years of age were found on investigation.

In the next ten-year age group, 15 to 24 years, of the 415 associates, 264, or 63.6 per cent, were children. Six, or 2.3 per cent, of these children had manifest tuberculosis. The onsets in 3 of these occurred after onsets in the parents. In the other 3, however, the same year of onset was given for both parent and child, so that the sequence could not be determined. The classifications of these cases were as follows: one minimal, 2 moderately advanced with positive sputum, one far advanced with positive sputum and 2 minimal arrested. None of the remaining 151 associates in this age group had manifest tuberculosis.

The relationship of the household associates in the next ten-year age group, 25 to 34 years, differed from that of the younger associates. Only 76 of the 220 associates 25 to 34 years of age were children. Two, or 2.6 per cent, of these children of index cases had manifest tuberculosis. Seventy-one consorts were included in this age group and 3 of these had the disease. There were 2 other cases found on investigation, one of a sibling and one of a brother-in-law of an index case. Unfortunately, the numbers of cases and associates in these groups were too small for conclusions.

For household associates 35 years of age and over, the data are presented according to relationship in table 3.

Of the 600 associates in this age group, nearly one-half, 276, were consorts. Of the consorts, 19, or 6.9 per cent, were found to have manifest tuberculosis at

the time of investigation. Ten, or 8.8 per cent, of the 114 other persons not related by blood had manifest tuberculosis. The other group with over 100 individuals was the group of parents. Of the 110 parents, 19, or 17.3 per cent, were found to have manifest tuberculosis. When the data in table 2 are combined by relationship, 27, or 12.9 per cent, of the 210 associates related by blood and 29, or 7.4 per cent, of the 390 not related are found to have had manifest tuberculosis. The difference between 12.9 and 7.4 per cent is of such an order that some significance can be attached.

In order to understand this difference, further study of the data is necessary. On subdivision according to sputum status it is seen that parents were frequently found to have the disease in both groups. The sputum status of the persons directing attention to the family appeared to have no relation to the prevalence of manifest tuberculosis in parents. Cases of tuberculosis accumulate in the

TABLE 3

Prevalence of manifest tuberculosis at the time of investigation in white household associates 35 years of age and over by relationship and character of index case

RELATIONSHIP	TOTAL			INDEX CASE SPUTUM-POSITIVE			INDEX CASE OTHER THAN SPUTUM-POSITIVE		
	Total	Manifest tuberculosis -		Total	Manifest tuberculosis		Total	Manifest tuberculosis	
		Number	Per cent		Number	Per cent		Number	Per cent
Total.....	600	56	9.3	160	28	17.5	440	23	6.4
Parent.....	110	19	17.3	39	7	17.9	71	12	16.9
Sibling.....	42	5	11.9	13	2	15.4	29	3	10.3
Child.....	41	1	2.4	16	1	6.2	25	0	—
Consort.....	276	19	6.9	53	11	20.8	223	8	3.6
Other.....	17	2	11.8	6	1	16.7	11	1	9.1
None.....	114	10	8.8	33	6	18.2	81	4	4.9

white population. Some of the parents developed the disease many years before and had a chronic form of the disease. Since the index case is the one directing attention to the family, it is evident that the tuberculosis in the parent was unknown to the Study until the examination was made. The onset of 11 of the 19 cases in the parents antedated that in the child directing attention to the family. Five cases in parents appeared to have developed subsequently to the onset in child. In the other 3, the sequence could not be determined, since the dates were not known. Of these 19 cases in parents, extensive as well as limited lesions were discovered; 6 were moderately advanced or far advanced, active, 4 were minimal, active, 3 moderately advanced, arrested and 6 were minimal, arrested. These results show that the examination of parents of cases is an excellent method of discovery of cases. They should be examined irrespective of the sputum status of the case in the child. They may be the source of the disease in the household or they may have acquired the disease subsequently to that in the child.

The study of the results in consorts of index cases according to sputum status reveals a different situation. Eleven, or 20.8 per cent, of the consorts of sputum-positive index cases had manifest tuberculosis while only 8, or 3.6 per cent, of the consorts of index cases other than sputum-positive had the disease. This difference indicates that the sputum status of the index case is probably related to the prevalence of manifest disease in consorts. Of the 11 cases in consorts of sputum-positive index cases, only 4 were said to have tuberculosis prior to onset of the disease in the marital partner, who was the index case; 4 were known to have a subsequent onset, one gave an onset during the same year as his marital partner, and in 2 the sequence was not given. Only 2 of the 8 cases in consorts of other than sputum-positive index cases gave onsets subsequent to that of the marital partner. Four of the cases in consorts were moderately advanced or far advanced, 3 were minimal, active, 2 moderately advanced, arrested and 10, or over one-half, minimal, arrested. Of the cases in consorts, the proportion with extensive lesions was slightly smaller than the corresponding proportion in parents. Of those in sputum-positive contact, only one of the 11 cases had a moderately advanced lesion, 3 had minimal and 7 arrested lesions. Although the numbers are small, with this subdivision it appears likely that the sputum status of the marital partner has some significance in the development of the disease.

From these findings two points can be made. Examination of household associates of index cases leads to the discovery of many cases in those related by blood to the index case. Cases with onsets many years prior to the onset of the index case as well as new subsequent cases are discovered. In those who are not related by blood, manifest tuberculosis is found, but it is found more frequently when there is known exposure to sputum-positive tuberculosis.

Since the prevalence rates in colored families for the three age groups did not differ significantly, the data for study of the findings according to relationship have been combined and are presented in table 4.

Twenty-one of the colored household associates were found to have manifest tuberculosis. In all but 2 the process was considered active at the time of investigation. These 2 were parents, age 57 and 65 years, with minimal arrested tuberculosis. Of the remaining cases, 5 were manifest childhood type, 8 were minimal, active, 3 were moderately advanced and 3 far advanced, active. Although a slight variation is seen in the percentages for those related and not related by blood, this may have no significance. Further data are needed for study of the significance of relationship to the index case in the colored population.

The prevalence of tuberculosis in consorts, siblings and parents of persons 15 years of age and over with reinfection type tuberculosis has recently been studied by Kallmann and Reisner (4). Cases of tuberculosis in their series of data, chiefly from white families, were also found more frequently in parents, siblings and co-twins than in consorts (table 5). The percentage of monozygotic co-twins (61.5 per cent) with reinfection tuberculosis was very high and is definitely suggestive that the genetic constitution is an important factor in the development of tuberculosis.

Recent analyses from Williamson County Tuberculosis Study also have shown the significance of familial susceptibility in the development of tuberculosis (5). As a result of this work, the extension of case-finding efforts to all living parents, siblings and children of persons known to have tuberculosis, irrespective of present household, has been recommended.

TABLE 4

Prevalence of manifest tuberculosis at the time of investigation in colored household associates by relationship and character of index case

RELATIONSHIP	TOTAL			INDEX CASE SPUTUM-POSITIVE			INDEX CASE OTHER THAN SPUTUM-POSITIVE		
	Total	Manifest tuberculosis		Total	Manifest tuberculosis		Total	Manifest tuberculosis	
		Number	Per cent		Number	Per cent		Number	Per cent
Total.....	517	21	4.1	326	19	5.8	191	2	1.0
Parent.....	68	6	8.8	49	5	10.2	19	1	5.3
Sibling.....	102	5	4.9	67	4	6.0	35	1	2.9
Child.....	139	6	4.3	96	6	6.2	43	0	—
Consort.....	44	1	2.3	25	1	4.0	19	0	—
Other.....	95	2	2.1	53	2	3.8	42	0	—
None.....	69	1	1.4	36	1	2.8	33	0	—

TABLE 5

*Cases of tuberculosis in relatives of twin index cases in New York State**

	TOTAL NUMBER	CASES	
		Number	Per cent
Husbands and wives.....	226	14	6.2
Parents.....	688	114	16.6
Half-siblings.....	42	4	9.5
Full-siblings.....	720	136	18.9
Dizygotic co-twins.....	230	42	18.3
Monozygotic co-twins.....	78	48	61.5

* Data from Kallmann and Reisner.

ATTACK RATES DURING OBSERVATION ACCORDING TO AGE GROUP

Since prevalence rates may be high due to the accumulation of cases over a period of time, incidence rates—attack rates during observation—are preferable for an exact study of the development of tuberculosis. As these families have been followed for periods varying from a few months to over nine years, new cases of tuberculosis have occurred during the period of observation. The modified life table method described by Frost (6) used in previous analyses of the Williamson County data has been used in calculating the person-years of life experience. The years of experience of associates in these white and colored families and the number of new manifest cases which have developed during this period of observation are given in table 6.

Thirty-five new cases of manifest tuberculosis were recorded in white associates who were followed for 9,486.75 person-years. The attack rate for these associates was 3.7 per 1,000. The rate of 0.9 per 1,000 in childhood (under 15 years) was very low, indicating that white children may have some immunity to manifest tuberculosis. Children in this age period, with the exception of the very young, usually have latent lesions of first infection type. Manifest disease rarely develops. In young adult life, 15 to 34 years of age, the attack rate of 6.9 per 1,000 was very high. In the third age group considered here, the attack rate of 3.2 per 1,000 was lower than in young adult life. These attack rates

TABLE 6

New cases of tuberculosis and attacks rates per 1,000 for white and colored household associates during the period of observation by age group and character of index case

AGE GROUP	TOTAL			INDEX CASE SPUTUM-POSITIVE			INDEX CASE OTHER THAN SPUTUM-POSITIVE		
	Person-years of life experience	New cases		Person-years of life experience	New cases		Person-years of life experience	New cases	
		Num-ber	Rate per 1,000		Num-ber	Rate per 1,000		Num-ber	Rate per 1,000
White									
Total.....	9,486.75	35	3.7	2,364.75	18	7.6	7,122.00	17	2.4
Under 15 years..	3,209.25	3	0.9	627.25	2	3.2	2,582.00	1	0.4
15-34 years.....	3,199.00	22	6.9	842.50	14	16.6	2,356.50	8	3.4
35 years and over.....	3,078.50	10	3.2	895.00	2	2.2	2,183.50	8	3.7
Colored									
Total.....	2,066.75	32	15.5	1,315.75	27	20.5	751.00	5	6.7
Under 15 years..	710.25	12	16.9	434.75	11	25.3	275.50	1	3.6
15-34 years.....	774.50	10	12.9	508.75	8	15.7	265.75	2	7.5
35 years and over.....	582.00	10	17.2	372.25	8	21.5	209.75	2	9.5

indicate that, in white families with a case of tuberculosis, young adults develop the disease more frequently than do children or adults 35 years of age and over.

The attack rates are also given in table 6 according to character of index case. The rate for white associates of sputum-positive index cases of 7.6 per 1,000 was over three times the rate of 2.4 for associates of other than sputum-positive index cases. In the former group the attack rate (16.6 per 1,000) was very high for young adults 15 to 34 years of age. In this age group household exposure to sputum-positive tuberculosis seems to have been responsible for a high attack rate. For the associates of other than sputum-positive index cases the rate for young adults 15 to 34 years of age was practically the same as the rate for those 35 years and over. In the age group 35 years of age and over, the attack rate for those exposed to sputum-positive index cases did not differ significantly

from the rate for those exposed to other than sputum-positive index cases. A few cases developed in this age period in both groups. There is no doubt that by this period of life all persons have been exposed to tubercle bacilli at some time but only certain ones develop the disease.

The attack rate for colored household associates of 15.5 per 1,000 was exceedingly high. The risk of developing tuberculosis in a colored family with a sputum-positive index case was very great—20.5 per 1,000 or 2 per cent per year.

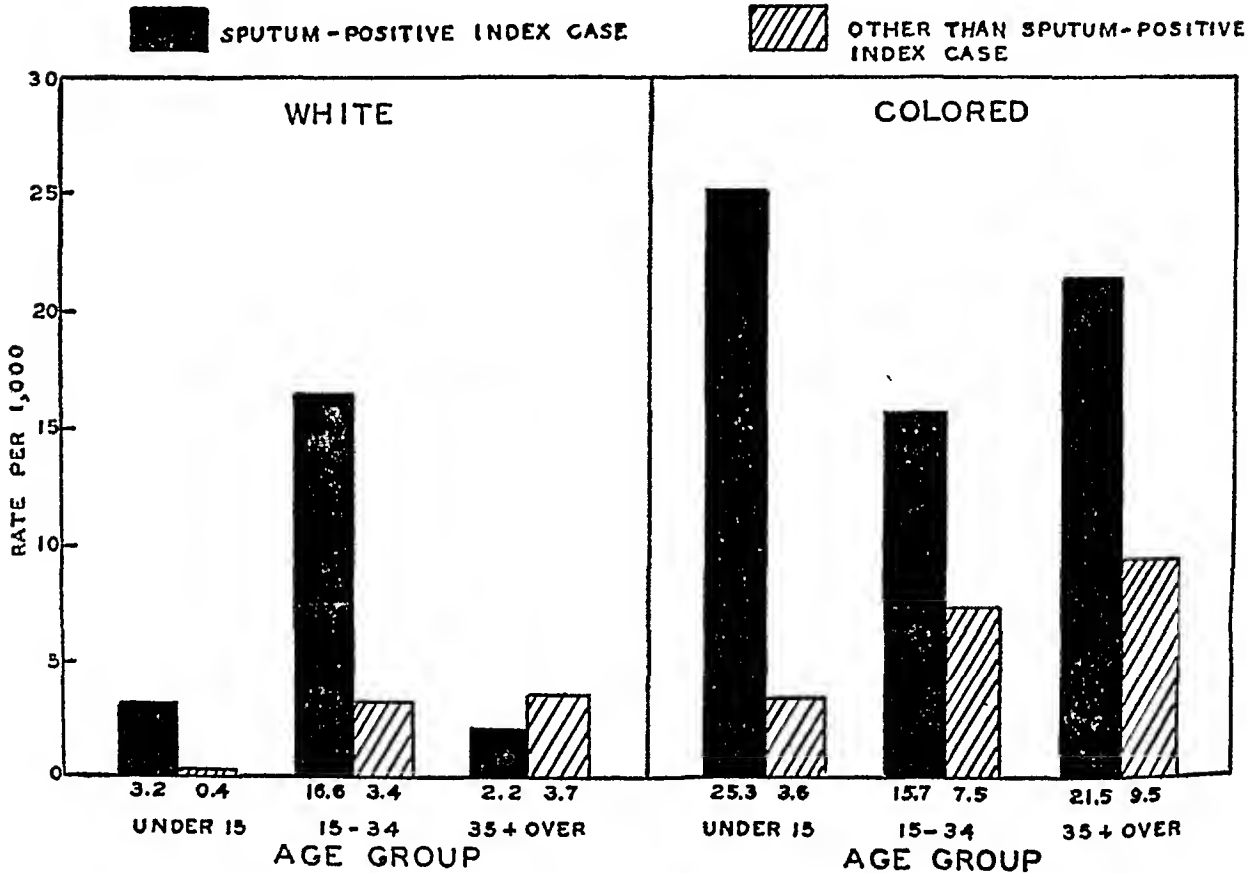


CHART 2. Attack rates per 1,000 of white and colored household associates during the period of observation by age group and character of index case.

Among these associates, persons of all ages developed tuberculosis with high attack rates in all three age groups. There did not seem to be any immunity to attack apparent in these colored persons in any age period. In a previous section the prevalence rates were shown to vary only slightly in these three age groups. Thus, considering both prevalence and incidence data, colored persons in all three age groups are at risk of developing tuberculosis; no immunity in any age period appeared to prevent the development of manifest tuberculosis.

These attack rates for the three age groups are shown in chart 2 for white and colored household associates according to character of index case. The great risk in young adult life 15 to 34 years of age in white associates of sputum-positive index cases and in colored associates of sputum-positive index cases in all age groups is evident.

ATTACK RATES IN ASSOCIATES DURING OBSERVATION ACCORDING TO RELATIONSHIP

Because of the variation in attack rates in white families by age groups, it is necessary to analyze the data according to relationship in these age groups. Since only 3 cases developed in the experience under 15 years of age, subdivision of this experience according to relationship will not be presented. For the other two age groups the attack rates will be given for consideration of the significance of the two factors—relationship and household exposure to tubercle bacilli.

The 3 cases which developed in persons under 15 years of age were in children of the index cases. The attack rate in these children who contributed two-thirds of the experience under 15 years of age (2,138.00 person-years) was 1.4 per 1,000. In the remaining 891.25 person-years of experience in this age group, no new cases developed.

TABLE 7

New cases of tuberculosis and attack rates per 1,000 of white household associates 15 to 34 years of age during the period of observation, according to relationship and character of index case

RELATIONSHIP	TOTAL			INDEX CASE SPUTUM-POSITIVE			INDEX CASE OTHER THAN SPUTUM-POSITIVE		
	Person-years of life experience	New cases		Person-years of life experience	New cases		Person-years of life experience	New cases	
		Num-ber	Rate per 1,000		Num-ber	Rate per 1,000		Num-ber	Rate per 1,000
Total.....	3,199.00	22	6.9	842.50	14	16.6	2,356.50	8	3.4
Parent.....	20.50	0	—	6.00	0	—	14.50	0	—
Sibling.....	261.50	7	26.8	103.00	6	58.3	158.50	1	6.3
Child.....	1,974.00	11	5.6	506.50	7	13.8	1,467.50	4	2.7
Consort.....	256.75	2	7.8	39.25	1	25.5	217.50	1	4.6
Other.....	312.50	2	6.4	84.50	0	—	228.00	2	8.8
None.....	373.75	0	—	103.25	0	—	270.50	0	—

For the next age group, 15 to 34 years, the data are presented in table 7. Over one-half of this experience (1,974.00 person-years) was of children. One-half of the experience of children was of children 15 to 19 years of age and three-fourths of children of the 15 to 24 year age group, leaving only one-fourth of the experience of children in the ten-year group 25 to 34 years. Many of the children, therefore, were in the early part of this period and had not passed through the period when attack rates are high.

Since the experience in the other groups of persons according to relationship is limited, interpretation of the data is difficult. Grouping of the experience, however, will be of value. For those not related by blood (consort and no relation) there were 630.50 person-years of experience; 2 new cases developed, giving an attack rate of 3.2 per 1,000 per year. As both of these cases were minimal and became arrested during the period of observation the disease could not be termed serious. For those related, there were 2,568.50 years of experience

and 20 new cases; the attack rate was 7.8 per 1,000. Seven of these cases were moderately advanced when manifest disease was discovered, 3 were far advanced with 2 dying in a short period of time from tuberculosis and one was minimal on discovery, but became moderately advanced later during observation. Of the remaining 9 who were minimal, active on discovery, 5 became minimal, arrested during observation and 4 were minimal, active at last observation. Thus, serious tuberculosis developed during the period of observation in these persons related to the index case. Although this experience is limited the results suggest that there is a difference between the attack rates for those related and not related and in addition serious tuberculosis appeared to develop among the related persons. Further data are necessary regarding these points.

The age of exposure to tuberculosis has been thought by some to be an important factor in the development of tuberculosis. Many of the children in this series necessarily had been exposed in childhood. Of the 11 children who developed the disease under observation, contact was reported to exist prior to 10 years of age for 8, one had contact at age 12, and 2 in adult life at 18 and 31 years of age. Of the 7 siblings who developed the disease, 3 reported contact under 10, and 4 gave contact in adult life at 23, 23, 28 and 30 years of age. One of the 2 others related by blood reported contact at birth and one at 21 years of age. Thus in all, 7 of the 20 cases, or 35 per cent, were not known to have had contact in childhood. Of the two consorts, neither one reported contact until adult life. Although the age of exposure may be a factor responsible for the development of the disease in related persons, not all these related persons are known to have had such exposure. Further material would be required to evaluate the effect of age of exposure among those related by blood.

In the next age group, 35 years and over, nearly two-thirds of the experience was of persons not related by blood to the index case—the consorts and those classed “none.” Ten new cases developed in 3,078.50 person-years of experience (table 8).

Only 2 of these cases were advanced, one in a consort and one in a sibling. The other 8 cases were minimal in extent and, of these, 6 became arrested during observation. Thus, the tuberculosis developing in persons 35 years of age and over who were associates of index cases was not serious in comparison with that in the younger age group. Only one of these, a consort, reported contact in childhood. Four cases developed in those related by blood in 1,086.50 person-years of life experience and 6 in those not related by blood in 1,992.00 years of experience. The attack rates of 3.7 for the first group and 3.0 in the second did not differ significantly.

Since the attack rates were high in all three age groups for colored associates, the data have been combined for study according to relationship (table 9).

The consorts as well as those related by blood had high attack rates in the colored group. Three of the 5 consorts died from tuberculosis during observation, one was far advanced and the other minimal at last observation. In the related persons, also, the course of the disease was unfavorable.

From the evidence of prevalence of tuberculosis and from these incidence

rates in colored households, related and nonrelated persons are susceptible to tuberculosis. Data by age indicated that there was no apparent resistance in exposed persons in the three age groups. The lack of resistance and failure of

TABLE 8

New cases of tuberculosis and attack rates per 1,000 of white household associates 35 years and over during the period of observation according to relationship and character of index case

RELATIONSHIP	TOTAL			INDEX CASE SPUTUM-POSITIVE			INDEX CASE OTHER THAN SPUTUM-POSITIVE		
	Person-years of life experience	New cases		Person-years of life experience	New cases		Person-years of life experience	New cases	
		Num-ber	Rate per 1,000		Num-ber	Rate per 1,000		Num-ber	Rate per 1,000
Total.....	3,078.50	10	3.2	895.00	2	2.2	2,183.50	8	3.7
Parent.....	521.50	1	1.9	192.00	1	5.2	329.50	0	—
Sibling.....	224.50	1	4.5	73.00	0	—	151.50	1	6.6
Child.....	273.75	1	3.7	105.75	0	—	168.00	1	6.0
Consort.....	1,432.75	5	3.5	317.50	0	—	1,115.25	5	4.5
Other.....	66.75	1	15.0	25.25	0	—	41.50	1	24.1
None.....	559.25	1	1.8	181.50	1	5.5	377.75	0	—

TABLE 9

New cases of tuberculosis and attack rates per 1,000 of colored household associates during the period of observation according to relationship and character of index case

RELATIONSHIP	TOTAL			INDEX CASE SPUTUM-POSITIVE			INDEX CASE OTHER THAN SPUTUM-POSITIVE		
	Person-years of life experience	New cases		Person-years of life experience	New cases		Person-years of life experience	New cases	
		Num-ber	Rate per 1,000		Num-ber	Rate per 1,000		Num-ber	Rate per 1,000
Total.....	2,066.75	32	15.5	1,315.75	27	20.5	751.00	5	6.7
Parent.....	280.75	4	14.3	207.00	4	19.3	73.75	0	—
Sibling.....	342.00	5	14.6	259.50	4	15.4	82.50	1	12.1
Child.....	532.00	13	24.4	253.50	13	36.8	178.25	0	—
Consort.....	177.00	5	28.3	94.50	4	42.3	82.50	1	12.1
Other.....	425.50	3	7.1	240.00	1	4.2	185.50	2	10.8
None.....	309.75	2	6.4	161.25	1	6.2	148.50	1	6.8

colored persons to show immunity to the disease may be largely responsible for the high tuberculosis death rate in the colored race.

SUMMARY

1. The data collected in the Williamson County Tuberculosis Study for the household associates of persons known to have tuberculosis are analyzed to show prevalence and incidence rates according to age and relationship. This analysis includes the records of the associates of 519 white and 111 colored index cases.

2. The prevalence rates for white associates increased from a low rate in individuals in the age group under 15 years to a high rate for those 35 years and over. The rates for the colored associates did not show this same distribution; relatively high rates were found in all three age groups.

3. The prevalence rates in white associates 35 years of age and over varied according to relationship to the index case and type of household exposure. While 27, or 12.9 per cent, of the 210 associates related by blood had manifest tuberculosis, only 29, or 7.4 per cent, of the 390 not related had the disease. Many factors may be operating to cause this difference in prevalence rates. The data are sufficient for emphasis on the examination of related persons irrespective of the amount of known exposure.

4. During the period of observation the attack rates for white associates were low in childhood and high in young adult life. For colored associates this variation was not seen; high attack rates were present in all three age groups. No apparent immunity to tuberculosis was noted for colored persons in any age group; in white persons, however, some immunity in childhood and in older adult life may be responsible for their failure to develop tuberculosis with household exposure to the disease.

5. For the age group 15 to 34 years, the attack rate for white household associates related by blood was 7.8 per 1,000 and for those not related 3.2 per 1,000. Although the experience is limited, this difference in attack rates in addition to the evidence from prevalence rates indicates that those related by blood to the index case appear to develop tuberculosis more frequently than those not related.

SUMARIO

1. A fin de obtener los coeficientes de frecuencia e incidencia conforme a edad y parentesco, analizáronse los datos colectados en un estudio de tuberculosis en el condado de Williamson en los allegados convivientes de personas que se sabía tenían tuberculosis. Este análisis comprende los protocolos de los allegados de 519 casos fichados en blancos y 111 en personas de color.

2. Los coeficientes de frecuencia para los allegados blancos han aumentado de una cifra baja en los individuos del grupo de menos de 15 años de edad, a una cifra alta en el de 35 años o más. Los coeficientes en los allegados de color no revelaron la misma distribución, encontrándose cifras relativamente altas en los tres grupos etarios.

3. Los coeficientes de frecuencia en los allegados blancos de 35 años o más de edad, variaron conforme al parentesco con el caso fichado y el tipo de la exposición casera. Aunque 27 (12.9%) de los 210 convivientes que eran parientes sanguíneos, mostraron tuberculosis manifiesta, sólo 29 (7.4%) de los 390 no emparentados la mostraron. Pueden intervenir muchos factores en esta diferencia en los coeficientes, mas los datos disponibles justifican el hacer hincapié en el examen de las personas emparentadas, haciendo caso omiso de la intensidad de la exposición conocida.

4. Durante el período de observación, los coeficientes de ataque en los allegados blancos fueron bajos en la infancia y altos en la juventud. En los de color

no se observó tal variación, habiendo coeficientes altos en los tres grupos etarios. No se notó ninguna inmunidad aparente a la tuberculosis en la gente de color a ninguna edad, pero en los blancos, la existencia de alguna inmunidad en la infancia y en la vida adulta más avanzada puede explicar por que no manifiestan tuberculosis tras la exposición a la enfermedad en el hogar.

5. En el grupo etario de 15 a 34 años, el coeficiente de ataque en los allegados convivientes blancos con parentesco consanguíneo fué de 7.8% por 1,000, y para los no emparetados de 3.2 por 1,000. Aunque la observación es limitada, esta diferencia en los coeficientes de ataque, unida a los datos derivados de los coeficientes de frecuencia, indica que los parientes consanguíneos del caso fichado parecen manifestar tuberculosis más frecuentemente que los no emparentados.

Acknowledgement is made of the valuable suggestions of Dr. J. A. Doull.

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TUBERCULOSIS AMONG MONTANA INDIANS¹

J. R. MCGIBONY AND A. W. DAHLSTROM

Indians living within the state of Montana are, for the most part, of the Plains Tribes which migrated westward with the encroachment of the whites into their customary habitat. The impact of the westward march of whites into areas to which the Indian had been forced is depicted in accompanying graph 1. The Indians are settled on lands set aside for the purpose by various treaties consummated in the middle and late nineteenth century. These treaties in many instances established the responsibility of the Federal Government for limited medical care. Prior to, and for some years after, the formation of the Department of the Interior in 1849, medical services to Indians were available only occasionally through the courtesy of Army post surgeons, as the administration of Indian affairs was a military function.

During the early years tuberculosis was recognized as a serious problem but funds and facilities were lacking to cope with the situation.

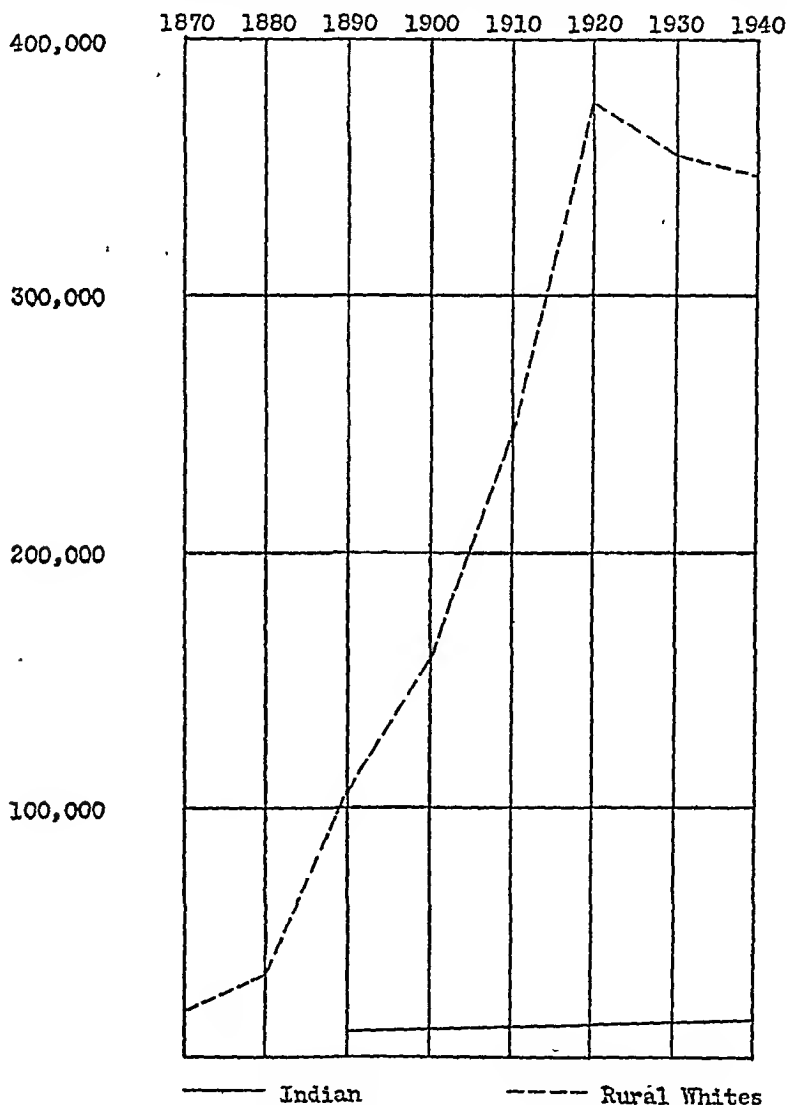
In subsequent years small general hospitals have been erected at the Blackfeet, Crow, Fort Belknap and Tongue River Agencies; while new hospitals are needed at Flathead and Fort Peck. However, none of these is planned to treat tuberculosis cases, hence such patients must necessarily be cared for elsewhere when beds are available. Consequently, little has been accomplished in hospitalizing tuberculous Indians, although considerable field work has been done. The state of Montana maintains a 260-bed sanatorium, usually overfilled, from which Indians have been excluded.

Indians constitute 2.7 per cent of the 555,185 total population of the state. There are relatively more children under the age of 20 among Indians than among whites because of a higher birth rate and a higher proportion of native born population. Because of economic status the general health problems are out of proportion to the ratio of population and tuberculosis is of major import. Indians reside principally in Glacier, Big Horn, Blaine, Roosevelt, Valley, Lake, Sanders, Choteau and Rosebud counties, on seven reservations, totaling 6,399,492 acres.

<i>Tribe</i>	<i>1943 Population</i>	<i>Post Office Address</i>
Total.....	16,219	
Blackfeet.....	4,292	Blackfeet Agency, Browning
Crow.....	2,200	Crow Agency, Montana
Flathead.....	2,779	Flathead Agency, Dixon
Assiniboine-Gros Ventre.....	1,666	Ft. Belknap Agency, Harlem
Sioux-Assiniboine.....	2,860	Ft. Peck Agency, Poplar
Cree.....	733	Rocky Boy's Agency, Rocky Boy
Northern Cheyenne.....	1,689	Tongue River Agency, Lamar

¹ From the Health Division, Office of Indian Affairs, U. S. Department of Interior, Chicago, Illinois.

The Indian population of Montana is increasing rather rapidly. Recently available complete figures reveal a birth rate of 33.9 and a death rate of 15.9 per thousand population in 1943. So, health and economic problems tend to increase unless active remedial measures are successful. In 1934 the Indian



GRAPH 1. Montana population, rural whites and Indians

population was 13,410; in 1943 it was 16,219, of which approximately 70 per cent were of more than one-half Indian blood.

A fairly large number of Indians have left the reservations to enter the military forces and to engage in war work. Fort Peck Agency had the largest percentage of enlistments of almost any group of young men in the country. Late figures are not available, but, of the first 72 Montana Indians examined for Selective Service, 26 per cent were rejected; none for tuberculosis, however (1). Indians remaining on the reservations have, of course, a correspondingly higher per-

centage of dependent children, old people and handicapped persons; so that, while increased income from absent workers and allotments to soldiers' families have been of considerable economic aid, the relative need has been higher since the war.

General incidence of disease will be the subject of another paper but it can be stated that it is comparable to other rural peoples of a like economic status. Differences in per centile distribution of deaths from all causes among the various age groups are shown in table 1, since they directly influence the incidence of tuberculosis. The differences in death rates from all causes, calculated from

TABLE 1
Montana Indian deaths (all causes by sex and age)
1934-1943

AGE GROUPS	ANNUAL AVERAGE NUMBER DEATHS 1934-1941			DEATHS PER 1000 POPULATION			PER CENT OF ALL DEATHS		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
Totals	292.5	155.0	137.5	19.7	20.1	19.3	100	52.9	47.1
Under 5	114.0	63.8	50.2	50.6	55.6	45.5	38.9	21.7	17.1
5-9	10.7	5.9	4.8	5.4	6.1	4.7	3.6	2.0	1.6
10-14	8.4	4.7	3.7	4.6	5.1	4.1	2.9	1.6	1.3
15-19	11.9	5.6	6.3	7.4	7.1	7.8	4.0	1.9	2.1
20-24	13.1	6.8	6.3	9.5	9.2	9.8	4.4	2.3	2.1
25-29	9.5	4.2	5.3	8.7	7.9	9.4	3.2	1.4	1.8
30-34	7.7	3.6	4.1	10.0	9.1	11.1	2.6	1.2	1.4
35-44	13.7	6.8	6.9	9.9	9.4	10.4	4.6	2.3	2.3
45-54	15.6	8.6	7.0	14.8	13.1	17.6	5.3	2.9	2.4
55-64	20.8	11.2	9.6	27.0	24.7	30.3	7.1	3.8	3.3
65-74	45.1	22.5	22.6	92.2	87.9	97.0	15.3	7.7	7.7
75 and over	21.2	11.1	10.1	91.8	96.5	87.1	7.3	3.8	3.5
Unknown	0.8	0.2	0.6	0.05	0.03	0.08	0.3	0.07	0.2

Source: Indian Office census rolls and vital statistics.

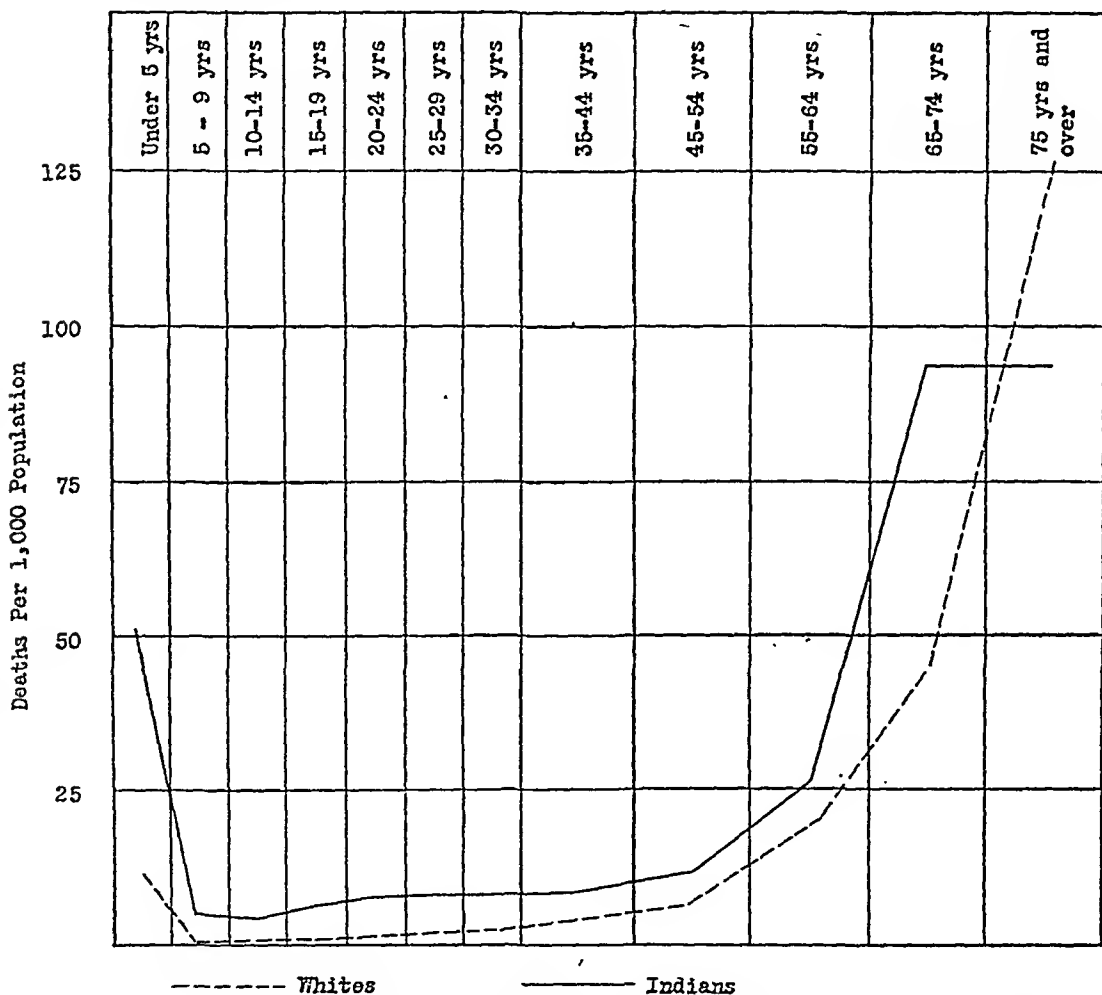
this table, among Indians and the white Montana population, which is predominantly rural, are shown in graph 2. Other than tuberculosis, diseases (particularly pneumonia) which contribute to a distressingly high infant mortality rate are of major importance.

Next to tuberculosis itself, the contributing factor of paramount importance to the high disease incidence among Indians is that of general economics. The rural slums in which many of them live are fully as conducive to high morbidity and mortality as the slums of the eastern urban areas. Sanitary facilities, proper excreta and sewage disposal, adequate and safe water supplies are lacking more often than not.

Housing is likewise a factor of major import, many of the large families (average 5 persons) occupy one or two rooms of small size, poorly constructed,

not insulated and badly ventilated, in a climate subject to a variation of temperature from 50 degrees below to 110 above zero.

Income, principally from livestock and agricultural sources, varies from an annual (1942) average per family of \$1,473 at Crow Agency to \$711 at Rocky Boy's, with a median of \$980 per family for all Indians of Montana, or approximately \$190 per person.

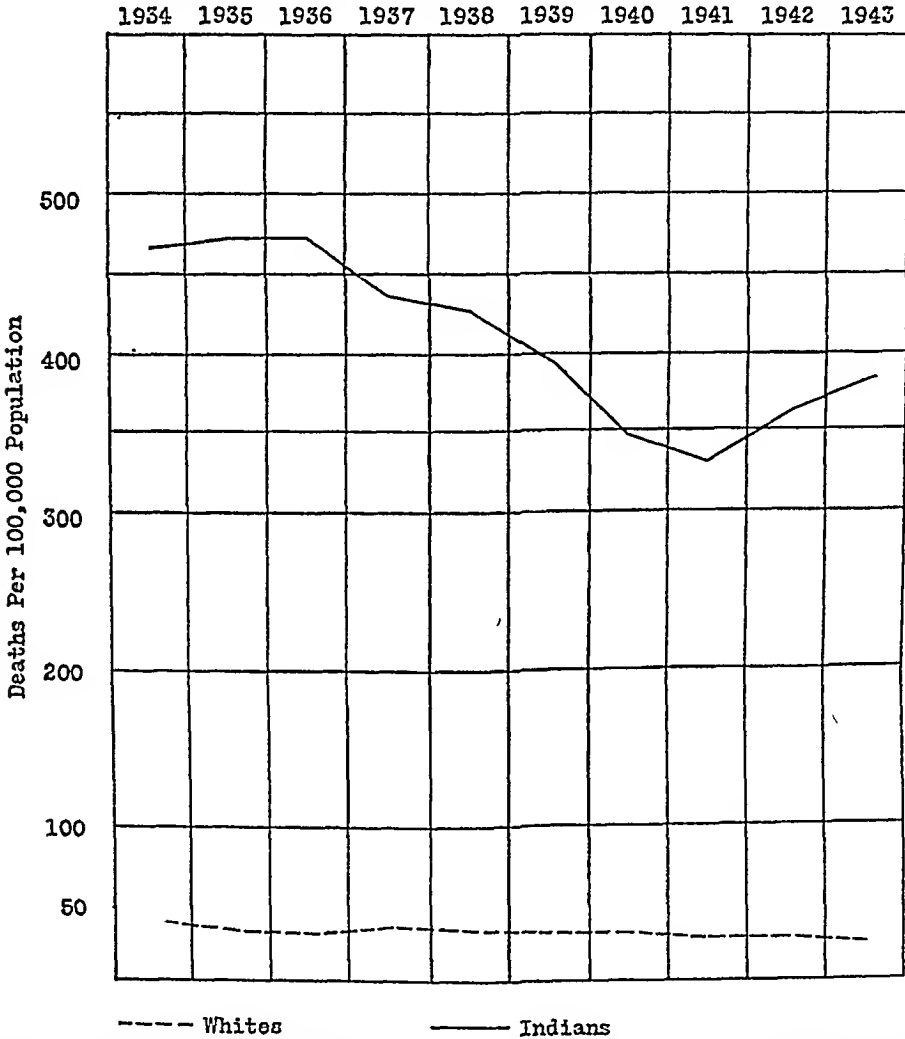


GRAPH 2. Montana deaths from all causes. Rates per 1,000 population among whites (1939-1941) and enrolled resident Montana Indians (1934-1943) by age groups.

While there has been a move toward individual and tribal betterment in the past few years, Indian society, including most of those of mixed blood, does not inculcate in the youth the habits of accumulation, of prudent forethought for the morrow or of thrift and continuous application. Instead, it teaches the young that magnanimity and generosity are the most desirable individual traits, that sharing is a social duty, that, conversely, thrift is akin to a vice. The nomadic hunting economy of the Indian produced a pattern of seasonal effort which persists to this day, giving rise to work habits which handicap the

Service in its efforts to weave the Indian into the fabric of an intensely acquisitive society.

Add to these traits the strong personal democratic dignity of the individual Indian, a dignity which is continuously offended by the peremptory commands of a society which accepts the whip of economic pressure as a necessary incentive, season these ingredients with eighty years of bitter historical resentment, and



GRAPH 3. Deaths from tuberculosis, all forms. Mortality rates per 100,000 population, whites and resident Montana Indians.

the result is a personality which does not fit into the present-day acquisitive industrial society.

It is regrettable that selfless magnanimity, generosity, broad charity, fearlessness, tolerance and a highly developed sense of personal dignity should be the characteristics which impede the individual possessing them in a society professing to be Christian, but it is a fact that these Indian traits handicap the possessor almost as much as the Indian habit of intermittent instead of continuous effort.

Education of Indians in Montana is largely through facilities of local public school districts, attended by whites and Indians, hence the educational level is theoretically that of rural whites. However, in light of language difficulties and cultural characteristics, with a native inherent reticence, the Indian is somewhat handicapped, as the school authorities have been unable to adjust curricula or make provisions for adaptation of teaching facilities to a problem in mental hygiene.

From the foregoing, one can visualize the difficulties faced by an organization attempting to inculcate an enhanced hygienic standard foreign to the historic concept of the race. Such standard was in fact possibly unnecessary to the mode of life enjoyed before the advent of the white man, who brought his trinkets, "fire-water," guns and, unwittingly, perhaps the most devastating death dealing factor ever confronting the Indian—the tuberculosis germ.

RACIAL IMMUNITY

Factors influencing the incidence of tuberculosis and the course of the disease among Indians are, as in all racial groups, many and varied. Economics, previously mentioned, is of extreme importance. Because of the high incidence, credence was long given to the theory that Indians as a race were unusually susceptible to tuberculosis. Extensive study has failed to substantiate this view for Indians in general at this time, and there is no reason to suspect that the Montana group would be otherwise. Burns (2) in Minnesota, Long and Hetherington (3) in Arizona, Korns (4) in New York, and others have noted in the present generation no marked differences in clinical types or X-ray appearance of tuberculosis among Indians from those found in whites; and resistance to the disease compared favorably with that of white persons.

Natural or racial immunity to tuberculosis has long been a controversial question. However, it is generally accepted at present that resistance to the disease by Indians is less than that shown by whites, but more than that possessed by the Negro race, when judged by the standards of morbidity and mortality rates and the X-ray appearance of lesions.

It can be assumed that no people have a racial characteristic which makes them peculiarly susceptible to the disease because of genotypic traits. Lack of exposure of any group, regardless of race, produces an extremely high incidence of tuberculosis which runs a more acute course when first introduced. After prolonged exposure, native immunity is manifest, with survival of stock resistant to the disease, and with a concomitant decline in the amount of clinical tuberculosis and the approach of saturation point of tuberculinization. With this there is noted a relative increase in pulmonary forms and an accentuation of chronicity.

This has happened among Montana Indians since the introduction of the disease by the whites, as revealed in the accompanying graphs and tables, which show reduced mortality rates and relatively smaller incidence of extrapulmonary forms.

Those of a higher degree of Indian blood have a much higher tuberculosis death rate than the others (see graph 4). Those of one-half and more of Indian blood furnished 70.9 per cent of the population and 94.9 per cent of the deaths due to tuberculosis. To give the ten-year (1934-1943) average annual rate of 403 deaths per 100,000 population, those of more than one-half Indian blood had a rate of 539.4 deaths per 100,000; while those with less than one-half Indian blood had a rate of only 85.3 deaths per 100,000 population. Thus,

All Degrees Of Indian Blood		POPULATION		DEATHS, ALL CAUSES		DEATHS, TUBERCULOSIS	
	MALES		51.9%		53.0%		51.4%
	FE- MALES		49.1%		47.0%		48.7%
One-Half Blood And Over	BOTH SEXES		70.9%		88.9%		94.9%
	MALES		36.9%		46.3%		48.8%
	FE- MALES		34.0%		42.6%		46.1%
Less Than One-Half Blood	BOTH SEXES		29.1%		11.1%		5.2%
	MALES		15.0%		6.7%		2.6%
	FE- MALES		14.1%		4.4%		2.6%

GRAPH 4. Percentage distribution of population, deaths from all causes, and deaths from tuberculosis among enrolled resident Montana Indians, by sex and degree of blood, 1934-1943.

the rate for those of higher degree of Indian blood is approximately sixteen times that of the white population and the rate for those with less Indian blood is only two and one-half times that of whites (see table 6).

The pulmonary forms of tuberculosis in these ten years constituted 80.7 per cent of the total cases among Indians; with 2 per cent involving bones and joints; the remaining 17.3 per cent are general miliary, meningeal or other extrapulmonary forms. These latter forms contribute in large measure to the tuberculosis deaths found in the infant and preschool groups. Those having more than one-half Indian blood showed an extrapulmonary rate more than

four times that found among Indians with less than one-half Indian blood. The trend is toward a relative decrease in these forms.

The incidence of deaths from tuberculosis varied rather widely among the seven Indian groups in Montana (see graph 5). The highest rate was found at Tongue River, with 807.7 deaths, and the lowest at Rocky Boy's Agency, with 229.7 deaths per 100,000 population. The annual average for all Montana Indians was 403 deaths per 100,000 population. The Northern Cheyenne Indians of the Tongue River Reservation have had sufficient exposure to develop

RESERVATIONS	POPULATION	DEATHS ALL CAUSES	DEATHS TUBERCULOSIS
BLACKFEET	26.0%	22.6%	27.7%
FORT PECK	17.5%	15.7%	16.9%
FLATHEAD	17.3%	16.2%	14.7%
CROW	13.7%	15.2%	9.0%
TONGUE RIVER	10.5%	17.5%	21.1%
FORT BELKNAP	10.0%	8.1%	8.2%
ROCKY BOYS	4.4%	4.5%	2.5%

GRAPH 5. Percentage distribution of population, deaths from all causes, and deaths from tuberculosis among enrolled resident Montana Indians, 1934-1943, by reservation.

much tuberculosis but have had less opportunity and inclination to adopt white standards of living. They are the only group that furnishes a considerably higher proportion of tuberculosis deaths than would be expected from the population ratio. Tongue River, with 10 per cent of the Indian population, had 21.1 per cent of the tuberculosis deaths from 1934 through 1943. Fort Belknap, with a comparable population ratio, but more closely associated with white society and standards and a higher per capita income, furnished only 8.2 per cent of the deaths from tuberculosis during this same period (see tables 4 and 5).

TABLE 2
Montana Indian mortality from tuberculosis (1934-1943)

	ANNUAL AVERAGE NUMBER TUBERCULOSIS DEATHS			ANNUAL AVERAGE TUBERCULOSIS DEATHS PER 100,000 POPULATION			PER CENT TUBERCU- LOSIS DEATHS BY AGE GROUPS	PER CENT TUBERCU- LOSIS IN DEATHS FROM ALL CAUSES
	Total	Male	Female	Total	Male	Female		
Totals	59.8	30.7	29.1	403.0	398.7	407.7	100	20.4
Under 5	13.5	7.5	6.0	599.5	653.3	543.5	22.6	11.8
5-9	4.0	2.2	1.8	200.5	227.0	175.4	6.7	37.4
10-14	4.3	2.6	1.7	237.0	283.2	189.7	7.2	51.2
15-19	7.5	3.2	4.3	469.3	404.0	533.5	12.5	63.0
20-24	8.2	3.9	4.3	593.3	529.2	666.7	13.7	62.6
25-29	4.2	1.8	2.4	383.2	339.0	424.8	7.0	44.2
30-34	3.1	1.0	2.1	273.4	251.9	566.0	5.2	40.3
35-44	4.1	1.5	2.6	295.6	206.6	393.3	6.9	29.9
45-54	3.2	1.8	1.4	303.6	274.0	352.6	5.4	20.5
55-64	3.4	2.6	0.8	441.0	572.7	252.3	5.7	16.3
65-74	2.9	1.7	1.2	593.0	664.1	515.0	4.8	6.4
75 and over	1.4	0.9	0.5	606.0	782.6	431.0	2.3	6.6

Source: Indian Office census rolls and vital statistics.

TABLE 3
White mortality from tuberculosis by age and sex in Montana 1939-1941

AGE GROUPS	AVERAGE ANNUAL TUBERCULOSIS DEATHS 1939-1942			TUBERCULOSIS DEATHS PER 100,000 POPULATION			PER CENT TUBERCU- LOSIS DEATHS	PER CENT ALL DEATHS
	Total	Male	Female	Total	Male	Female		
Totals	173.4	138	35	32.1	47.7	13.9	100	3.19
Under 5	2.6	1.3	1.3	5.6	5.6	5.7	1.5	0.50
5-9	0	0	0	0	0	0	0	0
10-14	1	0.5	0.5	2.2	2.1	2.2	0.6	1.86
15-19	3	1.6	1.3	6.1	6.4	5.4	1.7	3.37
20-24	6	3	3	12.1	11.8	12.4	3.6	5.11
25-29	8.6	3.6	5	18.9	15.1	23.1	5.0	8.14
30-34	9	5.6	3.3	22.4	26.0	17.7	5.2	7.36
35-44	20	14	6	29.7	39.2	19.0	11.5	6.52
45-54	49.3	42.6	6.6	70.4	108.6	21.4	28.4	7.68
55-64	45	41.6	3.3	91.9	142.9	16.6	25.9	4.55
65-74	20.6	17.6	3	82.3	121.6	28.4	11.9	1.78
75 and over	8.3	7	1.3	81.9	118.7	30.7	4.8	0.65

Sources: "Tuberculosis in the U. S.," Vol. 1, 1943, National Tuberculosis Association; U. S. Bureau Census.

AGE AND SEX

The distribution of tuberculosis deaths by age groups among Montana Indians follows the generally accepted pattern except that the percentages are very high (22.6 per cent) in the infant and preschool groups (ages 0 to 5 years).

This is a reflection of the lower standards of living and the exposure to open cases of tuberculosis within the home. Over 25 per cent of the deaths occur in groups between the ages of 15 and 24 years. A relative increase is again noted after the age of 55 years. It is felt that the prevalence of disease in these older groups has a direct bearing on the high rates among children under the age of 5 years (see graph 6 and table 2).

Among the age groups of the white population of Montana the percentage distribution of tuberculosis deaths is quite different. But 1.5 per cent of the deaths occur among those less than 5 years of age. Over 70 per cent of the deaths occur among those 45 years of age and over (see graph 6 and table 3).

The influence of sex on tuberculosis mortality is not marked among Montana Indians. There is a slight predominance of deaths among males until the age

TABLE 4

Annual average tuberculosis mortality per 100,000 enrolled, resident Montana Indians; annual average tuberculosis deaths: by reservations, sexes, 1934-1943, inclusive

	ALL RESER- VATIONS	TONGUE RIVER	BLACK- FEET	FORT PECK	FLAT- HEAD	FORT BELK- NAP	CROW	ROCKY BOY'S
Annual average number tuber- culosis deaths.....	59.8	12.6	16.6	10.1	8.8	4.9	5.4	1.5
Annual average deaths per 100,000 population.....	403.0	307.7	430.6	390.1	337.7	330.9	266.1	229.7
Male deaths.....	30.7	5.9	8.8	5.3	4.3	2.8	2.6	1.0
Death rates.....	398.7	731.1	454.1	392.9	313.8	360.0	253.2	296.7
Female deaths.....	29.1	6.7	7.8	4.8	4.4	2.1	2.8	0.5
Death rates.....	407.7	889.8	406.9	387.1	364.8	298.7	279.4	158.2

of 19. From the age of 20 through 44, deaths are more common among females, and after the age of 45 the males again contribute a slight excess. Tuberculosis takes a heavy toll from all age groups of both sexes.

In sharp contrast, a similar comparison of the distribution of tuberculosis deaths among whites in Montana reveals a marked increase of deaths among males, and especially among those 35 years of age and over. This is a reflection on the effect of occupation, chiefly mining. The distribution of the deaths among white females has no outstanding characteristics.

A study of the place of death shows that, although there was a dearth of available facilities for the treatment of tuberculosis among Indians in Montana, 32.9 per cent of all deaths from this disease occurred in either hospitals or sanatoria. This is taken to indicate that the Indians as such are not adverse to accepting medical care if suitable facilities are available. There were, however, 401 deaths that occurred in the home during this ten-year period. When this fact is considered in the light of low family economy, overcrowding in poor homes and under substandard conditions, such a large number of deaths in

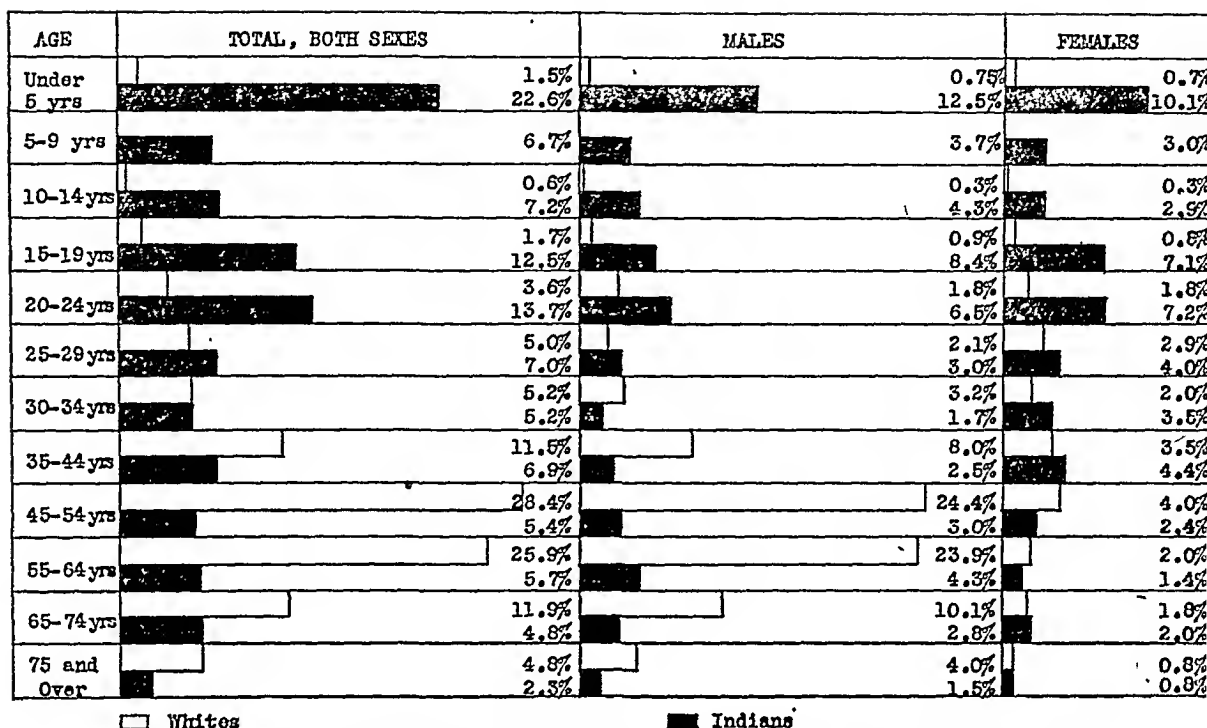
TABLE 5

Percentage distribution of population; deaths from all causes; deaths from tuberculosis; by reservations, sex and degree of Indian blood, enrolled resident Montana Indians, 1934-1943

	POPULATION			DEATHS, ALL CAUSES			DEATHS, TUBERCULOSIS		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
All Reservations.....	100.0	51.9	49.1	100.0	53.0	47.0	100.0	51.4	48.7
$\frac{1}{2}$ blood and over.....	70.9	36.9	34.0	88.9	46.3	42.6	94.9	48.8	46.1
Less $\frac{1}{2}$ blood.....	29.1	15.0	14.1	11.1	6.7	4.4	5.2	2.6	2.6
Tongue River.....	10.5	5.4	5.1	17.5	8.9	8.6	21.1	9.9	11.2
$\frac{1}{2}$ blood and over.....	9.0	4.6	4.4	17.1	8.7	8.4	21.1	9.9	11.2
Less $\frac{1}{2}$ blood.....	1.5	0.8	0.7	0.4	0.2	0.2	—	—	—
Blackfeet.....	26.0	13.1	12.9	22.8	12.3	10.5	27.7	14.7	13.0
$\frac{1}{2}$ blood and over.....	15.7	7.9	7.8	19.5	10.3	9.2	25.7	13.7	12.0
Less $\frac{1}{2}$ blood.....	10.3	5.2	5.1	3.3	2.0	1.3	2.0	1.0	1.0
Fort Peck.....	17.5	9.1	8.4	15.7	8.0	7.7	16.9	8.9	8.0
$\frac{1}{2}$ blood and over.....	13.9	7.4	6.5	14.4	7.2	7.2	16.5	8.7	7.8
Less $\frac{1}{2}$ blood.....	3.6	1.7	1.9	1.3	0.8	0.5	0.4	0.2	0.2
Flathead.....	17.3	9.2	8.1	16.2	8.7	7.5	14.7	7.2	7.5
$\frac{1}{2}$ blood and over.....	7.8	4.2	3.6	11.5	6.0	5.5	12.3	6.0	6.3
Less $\frac{1}{2}$ blood.....	9.5	5.0	4.5	4.7	2.7	2.0	2.4	1.2	1.2
Fort Belknap.....	10.0	5.3	4.7	8.1	4.5	3.6	8.2	4.7	3.5
$\frac{1}{2}$ blood and over.....	8.4	4.4	4.0	7.7	4.3	3.4	8.1	4.7	3.4
Less $\frac{1}{2}$ blood.....	1.6	0.9	0.7	0.4	0.2	0.2	0.1	—	0.1
Crow.....	13.7	6.9	6.8	15.2	8.1	7.1	9.0	4.3	4.7
$\frac{1}{2}$ blood and over.....	11.5	5.8	5.7	14.4	7.6	6.8	8.8	4.1	4.7
Less $\frac{1}{2}$ blood.....	2.2	1.1	1.1	0.8	0.5	0.3	0.2	0.2	—
Rocky Boy's.....	4.4	2.3	2.1	4.5	2.4	2.1	2.5	1.7	0.8
$\frac{1}{2}$ blood and over.....	4.2	2.2	2.0	4.4	2.3	2.1	2.4	1.7	0.7
Less $\frac{1}{2}$ blood.....	0.2	0.1	0.1	0.1	0.1	—	0.1	—	0.1

the home contributes largely to the spread of tuberculosis among all Indians and accounts for the high mortality rates among the infant and preschool groups (see table 7).

Deaths from pulmonary forms of tuberculosis in the home are numerically and relatively higher than for other forms of this disease. There were 333



GRAPH 6. Percentage distribution of deaths from tuberculosis among Montana whites (1939-1941) and enrolled resident Indians (1934-1943) by sex and age.

TABLE 6

Montana Indian deaths from tuberculosis by form, sex, and degree of blood
(Annual average 1934-1943)

		1934-1943 AVERAGE ANNUAL POPULA- TION	ANNUAL AVERAGE NUMBER TUBERCULOSIS DEATHS 1934-1943				TUBERCULOSIS DEATHS PER 100,000 POPULATION			
			Total all forms	Pul- monary	Bone and joint	All other forms	Total all forms	Pul- monary	Bone and joint	All other forms
Total.....		14,837	59.8	48.3	1.1	10.4	403.0	325.5	7.4	70.1
All Indians	Male	7,700	31.6	25.1	0.7	5.8	410.0	326.0	9.1	75.3
	Female	7,137	28.2	23.2	0.4	4.6	395.1	325.1	5.6	64.5
Total.....		10,401	56.1	45.5	1.0	9.6	539.4	437.5	9.6	92.3
$\frac{1}{2}$ blood and over	Male	5,372	29.3	23.7	0.6	5.0	545.4	441.2	11.2	93.1
	Female	5,029	26.8	21.8	0.4	4.6	532.9	433.5	8.0	91.5
Total.....		4,336	3.7	2.8	0.1	0.8	85.3	64.6	2.3	18.5
Under $\frac{1}{2}$ blood	Male	2,227	2.3	1.4	0.1	0.8	103.3	62.9	4.5	35.9
	Female	2,109	1.4	1.4	0	0	66.4	66.4	0	0

deaths (68.9 per cent) in the home during this ten-year period from pulmonary tuberculosis.

Those with one-half Indian blood and more, who died of tuberculosis at home, are both relatively and numerically more numerous than those of less than one-half Indian blood. The pulmonary form maintains its prominence among those with a higher degree of Indian blood (see table 6).

TABLE 7

Deaths from tuberculosis among enrolled resident Montana Indians—Total deaths from tuberculosis; deaths in hospitals or sanatoria—by form, sex, and degree of Indian blood. All reservations, 1934-1943

	ALL INDIANS			ONE-HALF BLOOD AND OVER			UNDER ONE-HALF BLOOD		
	Total tuberculosis deaths	Number tuberculosis deaths in hospital	Per cent in hospital	Total tuberculosis deaths	Number tuberculosis deaths in hospital	Per cent in hospital	Total tuberculosis deaths	Number tuberculosis deaths in hospital	Per cent in hospital
Total all forms.....	598	197	32.9	561	183	32.6	37	14	37.8
Males.....	307	104	33.9	293	97	33.1	23	7	30.4
Females.....	291	93	31.9	268	86	32.1	14	7	50.0
Pulmonary.....	483	150	31.1	455	138	30.3	28	12	42.9
Males.....	251	75	29.9	237	70	29.5	14	5	35.7
Females.....	232	75	32.3	218	68	31.2	14	7	50.0
Bone and joint.....	11	5	45.4	10	5	50.0	1	—	0.0
Males.....	7	3	42.9	6	3	50.0	1	—	0.0
Females.....	4	2	50.0	4	2	50.0	—	—	—
Other forms.....	104	42	40.4	96	40	41.7	8	2	25.0
Males.....	58	26	44.8	50	24	48.0	8	2	25.0
Females.....	46	16	34.8	46	16	34.8	—	—	—

Sex does not seem to play any outstanding rôle in relation to place of death from this disease. It is found that 203 (66.1 per cent) males and 198 (68.1 per cent) females died of tuberculosis in the home.

INCIDENCE

It is not possible at this time to state definitely the case-load of tuberculosis among the Indians of Montana. It is estimated that about one-third of all the Indian population has been given X-ray examinations for tuberculosis. On some reservations well over 50 per cent of the population have been so examined, but a considerable amount of X-ray examination of the general Indian population still remains to be done.

X-ray examination of over 50 per cent (1,847 persons) of the Blackfeet population, in 1937, revealed 58 cases of active tuberculosis, or an incidence of 3.14 per cent of those examined. This is consistent with similar surveys of other Plains groups (Pine Ridge, South Dakota), where X-ray examination of 6,325 or 79.1 per cent of the population revealed 3.59 per cent to have active tuberculosis. By applying the above percentages to the 1943 Montana Indian population (16,219), one should expect to find approximately 550 cases of significant active tuberculosis among the Indians in the state. Assuming this figure to be correct, the ratio of cases to average annual deaths is approximately 9 to one. To achieve a minimum standard of two beds for each annual death there should be at least 120 Indians under treatment at all times. At present, seldom more than 60 beds are available for the treatment of Montana Indians at any one time, and then at the expense of facilities in other states which are needed for local cases.

Applying this ratio of 9 cases for each annual death among the white population, it is noted that the 173 annual deaths would indicate about 1,500 cases of active tuberculosis, or approximately 0.3 per cent of the total population, a case rate one-twelfth of that among Indians.

For a number of years it has been a standing order in Indian Service hospitals that each patient admitted be given an X-ray examination of the chest. Since the rate of hospitalization of Indians is almost three times that of the general population, this gives an excellent opportunity for case-finding. Also, school children are examined at least once annually, and numerous well attended out-patient clinics are held. Because of these and other factors, it is believed that a larger proportion of cases of tuberculosis are discovered and reported than among white groups. Card records are maintained of all cases and, where a sufficient medical staff is available, on family groups in contact with the disease.

TUBERCULIN TESTING

Extensive tuberculin testing has been performed in the Indian Service over many years. However, in the principal phases of case-finding with which we have been primarily concerned, it has been learned through experience that the incidence of reactors is so very high, at least among the susceptible age groups, that it has not been considered advisable to spend much time or effort in generally using the procedure. The reactors rapidly approach 100 per cent after the age of 20. The earliest figures for Montana in which tuberculin testing by age groups was shown were reported by Crouch (5) in 1931, in which only those of school age were listed as follows:

	<i>Tuberculin Tested</i>	<i>Indians</i>		<i>Whites in Adjacent Communities</i>		
		<i>Positive</i>	<i>Per Cent</i>	<i>Tuberculin Tested</i>	<i>Positive</i>	<i>Per Cent</i>
Totals.....	2,043	1,244	60.9	1,410	318	22.5
Blackfeet.....	535	300	56.1	102	53	52.0
Ft. Peck.....	457	263	57.5	503	86	17.1
Ft. Belknap.....	358	205	59.2	328	58	17.7
Rocky Boy's.....	81	49	60.4	1	1	—
Crow.....	314	193	61.4	465	116	24.9
Tongue River.....	298	234	78.5	11	4	36.4

<i>Age Groups</i>	<i>Tuberculin Tested</i>	<i>Indians</i>		<i>Whites in Adjacent Communities</i>		
		<i>Positive</i>	<i>Per Cent</i>	<i>Tuberculin Tested</i>	<i>Positive</i>	<i>Per Cent</i>
5-9	791	423	53.4	440	83	18.9
10-14	965	621	64.3	632	147	23.3
15-19	274	204	74.5	325	84	25.8

The only other figures giving age groups were prepared by Hamernik (6) in 1941, of the tuberculin reactions among school children in the vicinity of the Crow Reservation:

<i>Age Groups</i>	<i>Tuberculin Tested</i>	<i>Crow Indians</i>		<i>Whites in Crow Area</i>		
		<i>Positive</i>	<i>Per Cent</i>	<i>Tuberculin Tested</i>	<i>Positive</i>	<i>Per Cent</i>
Total	446	188	42.1	908	43	4.7
5-9	233	72	30.9	420	13	3.1
10-14	175	93	53.1	365	17	4.1
15-19	38	23	60.5	123	13	10.5

Tuberculin testing in the Indian Service, when performed as a routine measure in case-finding by agency physicians and public health nurses, is done by the patch test or by the intracutaneous injection of a solution of PPD, using 0.000,02 mg. as the first dose since severe reactions occasionally occur. Those who do not react to the first dose after an interval of forty-eight hours are given 0.005 mg. It has been noted that, since tuberculin testing, particularly among school groups, offers an excellent opportunity for health education, the patch test appears to be preferable and its results fully as reliable and accurate.

Higher sensitivity to tuberculin in Indians has been shown in previous studies, particularly by Aronson (7).

Because of the lack of adequate administrative, nursing and clerical personnel, much of the information on Indian health has not been tabulated in correlated form. This paper is the first in a series designed to make such facts available in order that an analytical and more efficient approach toward solution of the problems may be undertaken.

During the war, with large numbers of physicians, nurses and others away from the Service, it may not appear promising that rapid corrective measures will be instituted. However, plans have been and are being made to establish effective procedures for curbing the menace of tuberculosis and other conditions detrimental to Indians and to whites in the same communities. The Montana Tuberculosis Association has exhibited a keen interest in the problem and much credit is due them for bringing it to the attention of the public. Likewise, the State Board of Health, State Medical Association, Federation of Women's Clubs and other organizations and individuals have assisted materially.

Goals in regard to tuberculosis, which would assist in promoting all health and related problems, include:

1. Adequate and competent personnel to examine and treat all Indians, in coöperation with local health authorities, and to secure and maintain proper knowledge of health conditions. This would include, at least, a part-time

director of tuberculosis activities and a sufficient field staff to execute the program.

2. Provision of adequate sanatorium facilities, either state or federal. It is estimated that a minimum of 100 to 150 beds for Indians would be satisfactory as a beginning.

3. A sustained program of health education would be a necessary concomitant of any tuberculosis campaign. This would be directed not only at the Indian but at the whites as well to encourage all to accept a community, county and state responsibility for common problems.

4. A program designed to elevate the general economic level and living standards of the Indian must be the coordinated effort of all divisions of the Service and State authorities, and so planned, with sympathetic and proper understanding of Indian personality traits, as to assist him in every way to shoulder some of the responsibilities of development.

SUMMARY

A ten-year (1934-1943) study of the 16,219 enrolled, resident Montana Indians on seven reservations under Federal supervision reveals that they constitute but 2.7 per cent of the total state population but present health problems out of proportion to the population ratio. The chief health problem is tuberculosis. Approximately 70 per cent of the Indians are one-half or more Indian blood and 95 per cent of deaths from tuberculosis occur in this blood group. Indian income is low (\$150 per person in 1942), housing is poor and crowded, sanitary facilities are lacking or inadequate. Pulmonary tuberculosis predominates (80.7 per cent). Over 22 per cent of deaths from tuberculosis occur among those under 5 years of age, and an additional 25 per cent occur among those between 15 and 24 years of age. Males contribute a slight excess over females except in the child-bearing age groups. Death rates are higher on reservations with low income and lower rates are found on reservations with better income and higher living standards. Approximately two-thirds of all cases die within the home. Racial susceptibility, *per se*, has not been noted. On the contrary, it is believed that this racial group, without previous exposure to tuberculosis, since their forced migration to present habitat and the impact of white population over a period of years, has been sufficiently exposed to the disease so that now native immunity has become manifest with survival of resistant stock. Consequently, there have been a recent decline in the amount of clinical tuberculosis, an approach to saturation of tuberculinization, a relative increase in the pulmonary forms, and an accentuation of chronicity in the disease. About one-third of the Indian population has been given chest X-ray examinations. An estimated 550 cases of clinically significant active tuberculosis need institutional care. Practically no facilities are available for this purpose in Montana. At least 100 to 150 additional beds are needed immediately in the state to reach an acceptable minimum for this group. Adequate and competent health personnel is urgently needed to examine and treat these Indians. A sustained program of health education is a necessary concomitant

to the tuberculosis control program. A program designed to elevate the general economic level and living standards of the Indians by the coördinated efforts of the Federal and state authorities and others interested is essential. All efforts must be planned with a sympathetic and proper understanding of Indian personality traits to assist him in every way to shoulder some of the responsibilities of development.

SUMARIO

Un estudio decenal (1934-1943) de los 16,219 indios matriculados y residentes en 7 "reservas" del estado de Montana, bajo vigilancia Federal, revela que sólo constituyen 2.7% de la población total del estado, pero plantean problemas sanitarios que no guardan relación con la proporción que representan de la población. El principal problema higiénico es la tuberculosis. Aproximadamente 70% de esos indios poseen 50% o más de sangre india y 95% de la mortalidad debida a la tuberculosis recae en ese grupo sanguíneo. Los ingresos económicos de los indios son bajos (\$150 por persona en 1942), las viviendas son malas y están hacinadas, y las instalaciones sanitarias o faltan o son inadecuadas: La tuberculosis pulmonar predomina (80.7%). Más de 22% de la mortalidad debida a tuberculosis sobreviene entre las personas menores de 5 años y otro 25% entre las de 15 y 24 años. Los varones aportan un leve exceso sobre las mujeres salvo a la edad de la reproducción. La mortalidad es más alta en los sitios de bajos ingresos y más baja donde los ingresos son mayores y los hábitos de vida mejores. Aproximadamente dos terceras partes de todos los enfermos mueren en su domicilio. No se ha notado susceptibilidad étnica *per se*. Pero al contrario opínase que este grupo étnico, sin previa exposición a la tuberculosis dada su migración forzada a su residencia actual y el contacto con la población blanca durante un período de muchos años, ya ha estado suficientemente expuesto a la dolencia, de manera que se ha establecido la inmunidad natural con sobrevivencia de los resistentes. Por consiguiente ha tenido lugar recientemente una baja en la proporción de tuberculosis clínica; aproximación al punto de saturación de la tuberculización; un aumento relativo en las formas pulmonares; y acentuación de la cronicidad de la enfermedad. Aproximadamente a la tercera parte de la población india se le han ejecutado radiografías torácicas. Calcúlase que 550 casos de tuberculosis activa clínicamente importante necesitan asistencia sanatorial, en tanto que apenas hay medios para esto en Montana. Por lo menos necesitan 100 a 150 camas más en el estado para obtener un mínimo aceptable para dicho grupo. Necesítase con urgencia personal sanitario adecuado y competente para examinar y tratar a estos indios. Para la lucha antituberculosa precisa una obra sostenida de educación sanitaria, siendo también esencial un plan destinado a elevar el nivel económico general y los hábitos de vida de los indios mediante los esfuerzos coordinados de las autoridades Federales y estatales y de otros interesados. Hay que planear todos los esfuerzos con una comprensión apropiada de las características de la personalidad del Indio a fin de ayudarlo en todos sentidos a que asuma algunas de las obligaciones comprendidas en este programa.

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IMMOBILIZATION OF BOTH LUNGS¹

The Treatment of Pulmonary Tuberculosis in an Equalizing Pressure Chamber

ALVAN L. BARACH

Cessation of voluntary respiration takes place in the living subject when an adequate flow of oxygen into the lungs and elimination of carbon-dioxide is provided. That proprioceptive reflexes from the lungs do not stimulate lung movement under these circumstances may be seen by the apnea resulting from hyperventilation with 100 per cent oxygen. During this time the individual remains comfortable, free from cyanosis, without the impulse to breathe and with a motionless chest. The chemical factors in breathing may thus take precedence over proprioceptive reflexes. The purpose of the present studies in the treatment of pulmonary tuberculosis has been to secure immobilization of both lungs with the maintenance of the normal pulmonary ventilation and an adequate gas exchange.

The movement of the chest in ordinary breathing is such as to accomplish a transport of approximately 500 cc. of air in and out of the lungs eighteen times a minute. Under these circumstances the volume of the thorax is increased 500 cc. at the end of inspiration.

In 1926 a respirator was developed by Thunberg in which patients were enclosed within a chamber and exposed to an alternating pressure of one-sixth of an atmosphere twenty-five times a minute; this produced a movement of 500 cc. of air in and out of the lungs in the absence of voluntary respiration (1). The barospirator of Thunberg was designed as a method of artificial respiration for cases of respiratory paralysis due to poliomyelitis, morphine poisoning and similar entities that caused deficient respiration. In our studies with this type of apparatus in patients with pulmonary disease complete arrest of lung movement was not accomplished. When a small room was constructed in which an alternating pressure of 55 mm. Hg above and below the atmosphere was produced twenty-five times a minute, observation of patients enclosed within it showed clearly that the chest wall was compressed during the initial phase of the positive pressure cycle and expanded during the negative pressure cycle. The degree of chest movement markedly increased in cases in which bronchial constriction was present, such as bronchial asthma, pulmonary emphysema and pulmonary fibrosis.

The resistance of the tracheobronchial passageway was found to account for the observed fact that a higher pressure was applied to the outer chest wall than to its inner surface. In experimental observations on dogs, the difference in pressure between the inner and outer surface of the chest wall was found to be between 4 and 5 cm. of water during a pressure change of one-sixth of an atmosphere in a chamber (2).

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The development of the equalizing pressure chamber had as its purpose the application of an equal pressure on the inner and outer surfaces of the chest wall at the same time. When the body of the patient was separated from the head by an appropriate partition, including a collar about the neck, the arrival of air pressure to the chest wall could be satisfactorily delayed and reduced in degree. Air under pressure was first directed to the head compartment and then to the body end of the chamber through a constricted opening, so that the pressure on the chest wall was approximately 5 cm. less than that present in the head end of the chamber. Since the resistance of the tracheobronchial tree consumes in the average case 5 cm. water pressure, an equal pressure was exerted on the inner and outer surface of the chest wall. Furthermore, since the wave of air pressure arrived at the head end and was then subjected to a delay, probably less than one-tenth of a second, the air pressure wave was applied to the chest wall and to the upper and lower surfaces of the diaphragm at the same instant. In this way a motionless chest was obtained in the living patient, together with an absence of all voluntary breathing and the provision of a normal gas exchange in the lungs (2).

When animals were treated in this equalizing pressure chamber, after previous injection of asphyxial doses of nembutal, the arterial oxygen saturation was found to be maintained above 90 per cent with normal carbon-dioxide elimination, whereas when alternating pressure alone was used, as in the Thunberg type of respirator, the saturation fell to between 50 and 70 per cent with carbon dioxide retention (2).

In actual clinical trial of the Thunberg type of barospirator, not only was alternate compression and expansion of the chest present during the positive and negative cycles of pressure, but also the patient could not dispense entirely with voluntary respiration. At the end of a minute or two the impulse to inhale took place and caused a normal inspiration. Continuous arrest of normal breathing was, however, accomplished when patients were exposed to the equalizing pressure chamber, in which the same alternating pressure wave of 110 mm. Hg was produced but a partition between the head and chest end of the chamber made possible a simultaneous arrival of an equal pressure on both surfaces of the chest wall; the arterial oxygen saturation and the carbon dioxide content were found to be normal, even in patients with advanced pulmonary tuberculosis, in the absence of all voluntary respiration. The ability to dispense with the recurrent impulse to breathe required training which was achieved in one patient in a period of forty-five minutes and in the majority of patients in three to four hours. One patient required two to three days. A recent patient under study at this time, in whom there is evidence of marked pulmonary fibrosis and emphysema, manifests alternating expansion and compression of the lungs and inability to give up all voluntary respiration. Of 10 patients who have been treated for four months, in some cases for several courses of four months each, arrest of lung movement has been obtained in all.

Arrest of lung movement does not appear to create discernible changes in the circulation. Although inspiration is said to be effective in aiding the inflow

of blood into the right heart in ordinary breathing, the absence of inspiration results in no apparent change in venous pressure, pulse rate, arterial blood pressure or circulation time. The effect on the ear drum of the oscillating pressure is similar to swift ascent and descent from high altitudes. The sensation can be minimized by placing a sponge-rubber covering over the ears. The majority of patients after the first day or two prefer to dispense with the sponge-rubber covering and become oblivious to the sensation. However, wearing of the sponge-rubber ear covering is recommended in order to reduce the changing of the position of the drum to a minimum.

The effect of equalizing pressure chamber therapy on the central nervous system was unexpected and of considerable interest. When voluntary respiration is abandoned, the impulse for movement of the voluntary muscles in the extremities or any part of the body is strikingly diminished. A man may lie in the chamber for periods as long as one to four hours without changing his position or moving his hands from side to side. Observation of these patients at ordinary bed-rest during periods when they are not in the chamber reveals the marked frequency of spontaneous movements in the voluntary musculature; they wish to read, listen to the radio or smoke, and can remain absolutely quiet for relatively short periods. However, as soon as they are placed in the equalizing pressure chamber and undergo arrest of lung movement, the desire to move their hands or legs is either absent or very much less than when breathing normally. Patients are able to forego the pleasure of smoking and to relax in the chamber in a way which is impossible when they are at ordinary bed-rest. Just what the mechanism is which explains the freedom from the necessity of the common and easily observable forms of movement of the voluntary musculature cannot be adequately discussed at this time.

The provision of this type of local lung rest, in which movements of the lungs do not take place, or if they do occur are of minimal degree compared to the known excursions of voluntary breathing, favors the process of healing by reducing changes in the physical state of the tuberculous process; in addition, it has a specific effect on those cavities in which a check-valve action is present. The maintenance of cavity and its enlargement in some patients with pulmonary tuberculosis is dependent upon a constricted entrance to the cavity, a bronchus or bronchiole being of relatively small diameter compared to the volume of the cavity. Under these circumstances, an inspiration is followed by enlargement of the cavity with inflow of air into it; during expiration there is a delay in the exit of air from the cavity through the narrowed bronchus, with probable increased pressure on the walls of the cavity.

In equalizing pressure chamber therapy the patient is instructed to stop breathing at the end of a normal expiration, but not a full expiration. In some patients a chest position midway between normal inspiration and normal expiration is most comfortable. The cavity is then not exposed to recurrent inspiratory enlargement since during both positive and negative pressure phases the chest is motionless. This would obtain as long as the entrance to the cavity was not obstructed. In actual test of the method on patients with cavities of con-

siderable size, the disappearance of cavity has been explained by the hypothesis that immobilizing the lung prevented inspiratory enlargement of the cavity. Other mechanisms may be present, as yet undetermined.

Patients are generally treated in this chamber from 8:30 in the morning to 9:30 at night, being removed for meals. A course of therapy in most instances consists of four months of this program.

Although a room was originally used with a box inside the chamber, in which the head was free and the body of the patient enclosed to obtain equalizing pressure, a simplified apparatus is now employed in which the entire patient is in a chamber that looks like the ordinary respirator except that the head is enclosed as well (figures 1 and 2).

The chamber employs atmospheric air and may be run on the ordinary type of alternating current. Provision for cooling the head end of the chamber is made in this apparatus, as in the previous one (3, 4).²

In 1940 a preliminary report was made of 5 patients with advanced pulmonary tuberculosis who were treated by immobilization of the lungs (5). Patients were selected in whom no other type of treatment, including pneumothorax and thoracoplasty, was considered desirable. Furthermore, all patients had had previous treatment with bed-rest without significant improvement. The response of 4 out of 5 patients justified the conclusion that immobilization of the lungs secured by residence in the equalizing pressure chamber aided the process of resolution in pulmonary tuberculosis. Four of the 5 patients showed a marked decrease in cough and expectoration, a fall in sedimentation rate and temperature to normal, a marked gain in weight and definite clearing of shadows in X-ray films, including the disappearance of the cavity and subjective improvement (6, 7).

In this report the follow-up results in these patients and the course of new patients treated since then will be presented. In a total of 10 patients with advanced pulmonary tuberculosis favorable results have been obtained in 6, and little or temporary improvement in 4. In the 6 patients who have been listed as benefited, one showed a significant favorable response with negative sputum for two years but requires additional treatment. The remaining 5 patients were considered well enough to work; one was lost sight of two years ago. The other 4 are now known to be at work for varying periods of time.

The only patient treated in this chamber who has been excluded from the present series is case 1 of the original report (6) who was in the equalizing pressure chamber for six hours daily for a two-month period. Although clinical improvement was shown, weight gain, decrease in cough and sputum, and clearing of mottled shadows below the cavities, no change in the actual size of the cavities resulted from this limited period of experimental trial of the method. The patient was ultimately transferred to a city convalescent out-patient department and was lost sight of. The series, therefore, here presented includes all treated cases. The patient under treatment at this time was one in whom, for a period

² The apparatus is now made by Mr. John H. Emerson, Cambridge, Massachusetts. Certain simplifications in the design of the pressure system make this model easier to operate.

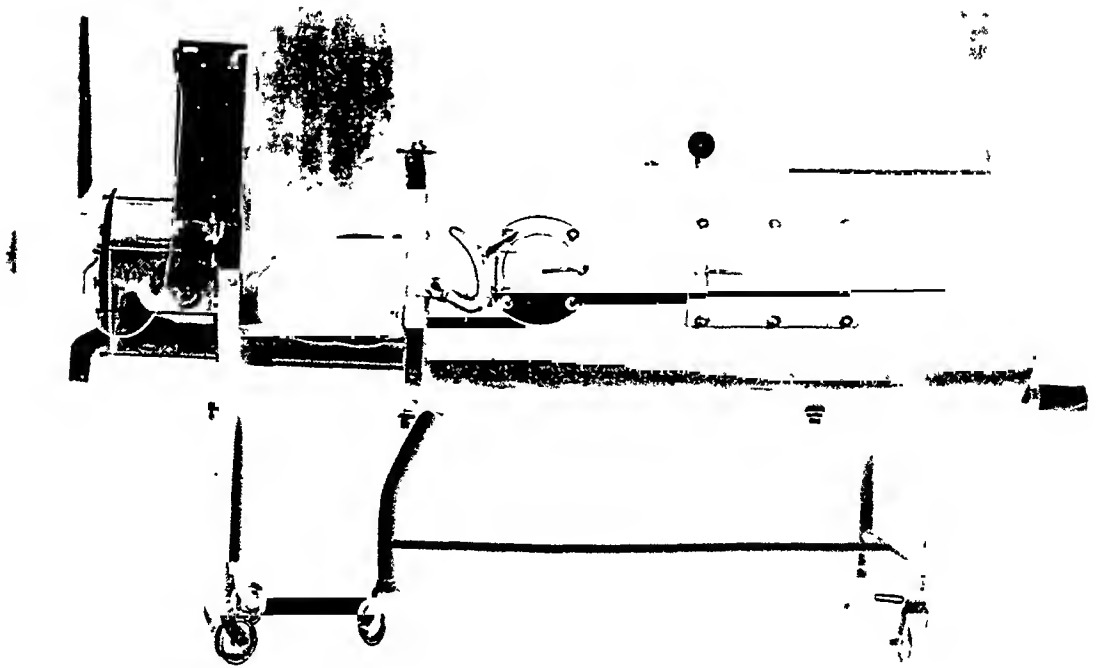


FIG. 1. (Upper) Equalizing pressure chamber.
 FIG. 2. (Lower) Equalizing pressure chamber with head compartment open.

of one month, immobilization of the lung had not been achieved because of the patient's marked increase in pulmonary ventilation and the presence of pulmonary emphysema. After a period of five months' oxygen treatment by nasal catheter, which was followed by a marked diminution in the volume of ventilation and increase in the breath-holding time from four to twenty seconds, the use of the equalizing pressure chamber was capable of producing a decrease in lung movement of approximately 75 to 85 per cent of that observed in ordinary normal breathing. A trial of the procedure is being made in this patient with advanced pulmonary tuberculosis and a large cavity in his left lung.

TABLE 1

Results of treatment of advanced pulmonary tuberculosis by immobilization of both lungs in an equalizing pressure chamber

NUMBER OF PATIENTS	FULL RECOVERY OR ARREST OF THE DISEASE	MARKED IMPROVEMENT WITHOUT COMPLETE ARREST OF DISEASE	SLIGHT IMPROVEMENT WITH NO SIGNIFICANT CHANGE IN COURSE
10	5 ✓	1	4

The case reports of the 10 patients will be given briefly as follows:

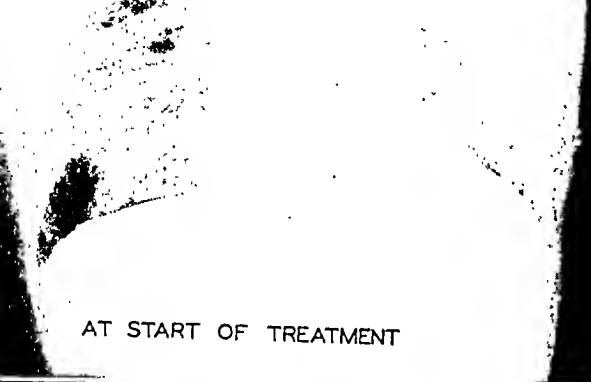
CASE REPORTS

Case 1: Man, age 38 years at the time of his original admission to the Presbyterian Hospital, May 6, 1938. This patient had clinical symptoms of pulmonary tuberculosis for a year prior to his admission to a municipal hospital, where he ran a low-grade temperature of 99 to 100°F. for two months. X-ray examination of the lungs showed a productive infiltration throughout both lungs, with dense infiltration and several small cavities in the upper half of the right lung, and many small cavities honeycombing the upper half of the left lung field. Examination of the larynx showed redness and edema of the epiglottis and the arytenoids. No change in the X-ray appearance was noted on bed-rest at this hospital; there was a weight gain of 4.5 pounds.

Immobilizing lung treatment was followed by a gain of 35 pounds in four months, a decrease in sedimentation rate from 70 to 15 mm. in one hour, a normal appearing larynx, decided clearing of infiltration of both lung fields. Under convalescent care he developed a negative sputum four months later, which has persisted. In September, 1939, X-ray examination of the lungs showed no infiltrative or cavitary lesions but some peribronchial fibrosis. The patient has been working over four years, except for a period of three months' bed-rest two years ago, when he manifested a recurrent infiltration in the right apex. This recurrence developed after a period of personal unhappiness during which he drank heavily and ate little. He recovered promptly on bed-rest, returned to work and has been clinically well since then to the present (October, 1944).

The accompanying illustration (figure 3) shows the lesions on May 31, 1938 before one course of four months' treatment and the follow-up film, December 3, 1941, over three years later. This patient's initial response to therapy was described in the original report (6) as case 2.

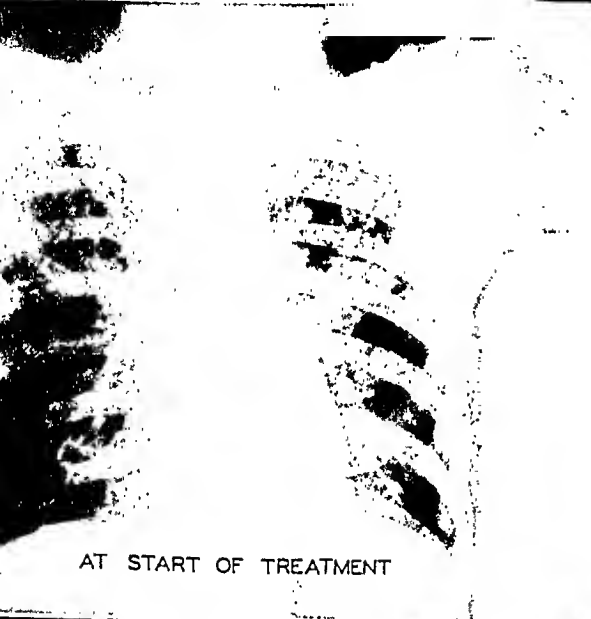
Case 2: Man, age 31 years at the time of his original admission to Presbyterian Hospital. Clinical symptoms of pulmonary tuberculosis had been evident for nine months prior to admission to a municipal hospital where he ran a fever of 100 to 101°F. for two months



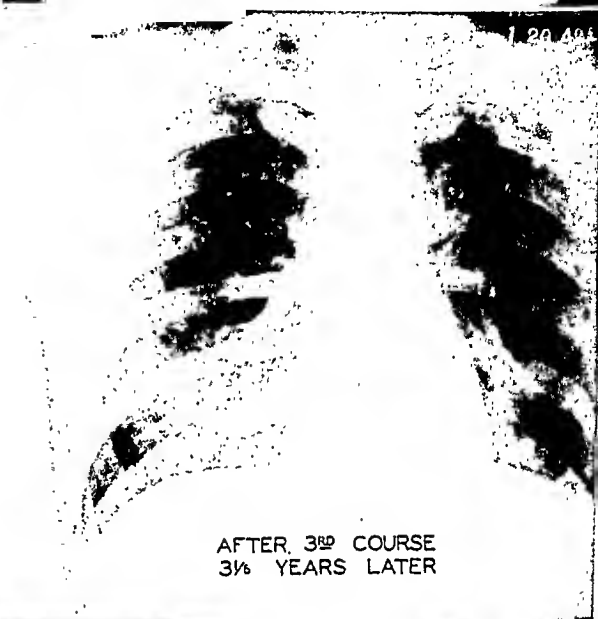
AT START OF TREATMENT



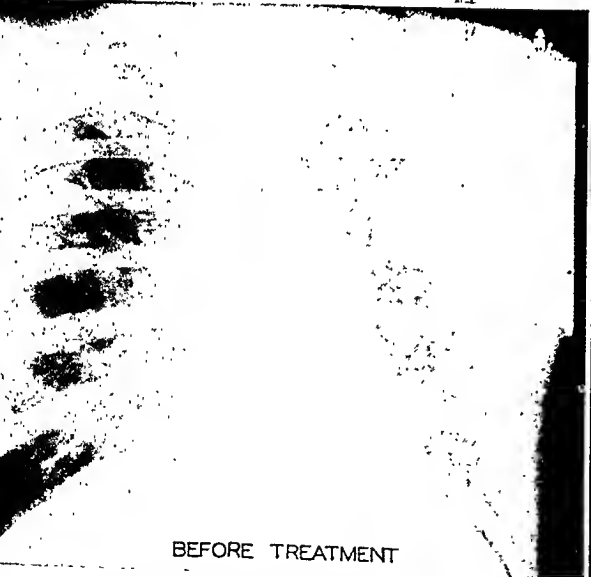
3 1/4 YEARS AFTER TREATMENT



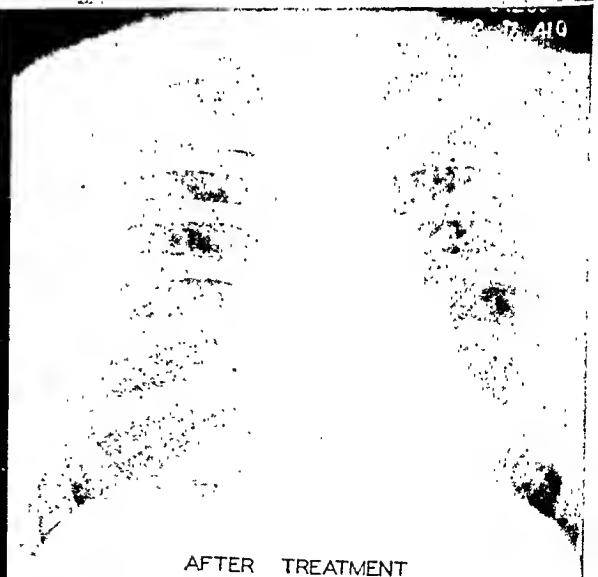
AT START OF TREATMENT



AFTER 3RD COURSE
3 1/2 YEARS LATER



BEFORE TREATMENT



AFTER TREATMENT

FIG. 3. (Top) Case 1. X-ray films at start of treatment, May 31, 1938 and three and a quarter years after one course of four months' therapy, December 3, 1941.

FIG. 4. (Middle) Case 2. X-ray films at start of treatment, November 30, 1938, and three and one sixth years later, January 20, 1942, after three courses of equalizing pressure therapy. Subsequent films in 1944 show no cavity or infiltration.

FIG. 5. (Bottom) Case 4. X-ray films before treatment, October 10, 1940, and after four months' therapy, February 17, 1941.

during bed-rest. There was a weight gain of 2 pounds. X-ray films of the chest showed an oval cavity at the level of the right second interspace, measuring 2.5 cm. in a vertical direction and 1.5 cm. transversely, with a smaller area of diminished density measuring 1.4 cm. in diameter just below it. On the left side, a cavity was present near the anterior chest wall at the level of the third rib which measured 2 cm. in diameter. There was another cavity above it measuring 1.7 by 1.2 cm. The upper three-fifths of the left lung showed dense shadows suggesting inflammatory exudate.

Following two and a half months of equalizing pressure therapy the cavities on the right side disappeared, and also the cavity near the left anterior chest wall at the level of the third rib was not seen. The multilocular cavity was replaced by a small area measuring 1.2 cm. in diameter. There was a definite diminution in the shadows suggestive of inflammatory exudate in both lungs. The patient gained 17 pounds, sedimentation rate decreased from 50 to 13 mm. in one hour, and the temperature became normal. After six months' convalescent bed-rest he was readmitted for a second course of equalizing pressure treatment because the remaining cavity in the left lung had increased in size to 2.4 by 3 cm. At the end of two and a half months of treatment the X-ray pictures showed a marked decrease in the size of the cavity both in stereoscopic and planigraphic films. A shadow of 0.6 cm. in diameter represented the remainder of the cavity.

The patient was originally admitted to Presbyterian Hospital on November 4, 1938. Following a second course of treatment he led a life of varied activity until November 14, 1940 when he returned to the hospital for a third course. The cavity in the left lung field had again increased in size to 3.5 by 2.5 cm. He was given a part-time position at the hospital as a technician and at the same time was treated for five hours a day in the equalizing pressure chamber. (The length of the previous courses was twelve hours daily.) On January 2, 1941, the X-ray film still showed the cavity to be present, only slightly smaller. He was allowed to continue living in a room outside the hospital but came in for treatment ten hours a day from February 15 to May 14, 1941. During this time X-ray examination showed a collapse of the cavity to 0.8 by 0.6 cm. Two months later the cavity had entirely disappeared. The accompanying illustration (figure 4) reveals the extensive lesions at the start of treatment, November 30, 1938, and their disappearance after three courses of equalizing pressure therapy, January 20, 1942.

During this third course of immobilizing lung therapy, sputum became consistently negative, and expectoration and cough completely disappeared. There was no recurrence of expectoration or cough, but an apparent reappearance of the small cavity, 0.8 by 0.6 cm. in the left lung field in October, 1941.

The patient was treated with inhalation of the nebulized spray of promin from October 25 to December 11, 1941, when he was allowed to return to work. The promin was diluted 50 per cent with tap water and nebulized by passing 5 liters of oxygen through the solution contained in a Vaponefrin nebulizer, the latter being held in the open mouth during quiet breathing. An average dose of 3 g. daily was inhaled, divided into four separate periods of administration. One month later X-ray examination revealed disappearance of the small apparently residual cavity.

Promin administered by mouth was shown to be effective in retarding the development of pulmonary tuberculosis in guinea pigs by Feldman, Hinshaw and Moses (8). Inhalation of the nebulized spray of promin was found to be similarly effective in guinea pigs in our laboratory (9), and the method was therefore tried in a few patients in this series.

Examination and culture of the contents of gastric lavage have been persistently negative for tubercle bacilli. The patient has continued clinically well and has been working for approximately three years.

The response to the first course of equalizing pressure therapy and the initial result of the second course were described in the original report (6) under case 3.

Case 3: Man, age 42 years at the time of his original admission to the Presbyterian Hospital. This patient had known tuberculosis for ten years, during which time he spent two to seven months at five different municipal hospitals. During the year prior to admission he had an acute exacerbation of symptoms with slight fever and loss of 14 pounds. The report of the X-ray examination was as follows: "There is an end stage caseous pneumonic tuberculosis involving the left upper lobe with marked thickening of the overlying pleura and retraction of the trachea toward this side. Areas of increased illumination are present in the infraclavicular region. There are areas of infiltration in the left mid-lung field. Exudative productive infiltration in the upper one-half of the right lung with occasional nodular infiltration in the right base." The larynx showed granulations over the true cords. A diagnosis of tuberculosis of the larynx was made.

After three months of treatment, thirteen hours a day, his weight increased from 133 to 154 pounds, the sedimentation rate decreased from 56 to 6 mm. in one hour, the larynx became normal and X-ray examination showed definite regression of the pulmonary infiltration in both upper lung fields, more marked in the left lung. The sputum was negative and continued to be negative in concentrated specimens at a municipal tuberculosis institution during the following two months. Gastric lavage specimens were also negative and the report then stated that X-ray examination did not reveal the presence of any cavity on either side but there were suspicious highlights present. Three months after discharge from Presbyterian Hospital his sputum was positive on one examination and a partial left pneumothorax was instituted, maintained for about a year and terminated May 30, 1941. Since discontinuance of the pneumothorax, repeated examinations of the sputum and gastric contents were consistently negative for one year and the patient was then discharged to obtain employment. X-ray examination showed thickening of the pleura over the left lung, fibrosis and some displacement of the heart and mediastinum into the left chest. No infiltrative lesions or cavities were visible in either lung field. He was well one and one-half years later but has been lost sight of for the past year and one-half. The immediate response to equalizing pressure therapy was described in the original report (6) as case 5.

Case 4: Man, age 44 years. One year before admission to Presbyterian Hospital he experienced onset of cough with several large hemoptyses, gradual weight loss, weakness and night sweats. Five and one-half months previously when he entered a city hospital he weighed 127 pounds. Pneumothorax was tried four months previously and abandoned. While at rest in bed his temperature fell from 102° to 99°F., he gained 30 pounds and his cough decreased. Examination of the lungs showed dulness, bronchovesicular breath sounds and many medium moist râles over the upper half of the left lung anteriorly and posteriorly. On X-ray examination a cavity, 3 by 4 cm., between the left first interspace and the second rib was described with probably smaller cavities below. The examination also disclosed dense exudative and productive infiltration on the left side and a scattered bronchogenic spread in the base. There was some improvement in the picture of the lesions by X-ray and a small decrease in the size of the cavity during the rest period at the city hospital over a five and one-half month period. However, at the time of his transfer from the city hospital to the Presbyterian Hospital, the cavity had increased in size, extending, according to planigrams, from the fourth to the twelfth centimeter levels, as measured from the X-ray table, the patient lying on his back. The sedimentation rate

was 42 mm. Thoracoplasty was not performed because of a mild febrile course, the presence of a slight lesion on the right side according to X-ray examination and the extent of tuberculosis on the left side. The cavity was large both in its transverse and vertical diameter and could be recognized by tubular breathing beneath the left clavicle.

At the end of four months of treatment the sputum was negative for tubercle bacilli and the temperature was flat. The sedimentation rate was 20 mm. in one hour. X-ray examination of the chest showed a marked decrease in the infiltration of the left lung field and an apparent disappearance of the cavity on both planigraphic and stereoscopic X-ray films. At the site of the original cavity there was an area, about 1 cm. in diameter, of increased density which suggested fibrous tissue or a collapsed cavity. Planigraphic films of this region, however, showed nothing that could be interpreted as the wall of a cavity. The accompanying photograph (figure 5) reveals the X-ray appearance of the lungs before the first course of treatment, October 10, 1940, and after four months of equalizing pressure therapy, February 17, 1941.

On return to the city hospital an initial sputum was positive but five later examinations of concentrated sputum were consistently negative. However, the cavity became definitely visible on subsequent X-ray pictures and, five months later, the patient returned to Presbyterian Hospital in July, 1941. During the five-month period when he was at the municipal hospital, his weight had decreased from 158 to 146 pounds. The sedimentation rate was 20 mm. after the first course and on readmission was 77 mm. at the end of one hour. Stereoscopic films of the chest, which in the former admissions had shown a collapse and virtual disappearance of the large cavity in the left upper lobe, revealed on readmission a large excavation, 5.3 cm. in diameter, containing a small amount of fluid, surrounded by a zone of infiltration 8 mm. in thickness in its outer portion and somewhat more in its inner portion. The amount of infiltration in the lung below the cavity had increased considerably, as compared with the film made at the end of his last admission. The planigrams confirmed the findings in the stereoscopic films.

During the following six months he had four months of equalizing pressure treatment. For three weeks of this period he inhaled the spray of 6 g. promin daily. This was stopped because of the development of an erythematous itching rash which cleared after a two-week period. In the accompanying photograph (figure 6) the cavity region on planigraphic X-ray examination is shown before (July 12, 1941) and after (January 30, 1942) the second course of four months of immobilizing lung therapy.

His weight increased to 181 pounds. The sedimentation rate decreased to 8 mm. in one hour. The sputum became consistently negative and during the last three months expectoration almost disappeared. Stereoscopic and planigraphic films showed a complete disappearance of the cavity. In the area where it was previously observed, there was seen a dense shadow 1.5 by 2 cm., which suggested that the cavity had been filled with fibrous tissue. There was marked clearing of the infiltration below the cavity.

During one period of two weeks the patient resided in the equalizing pressure chamber for twenty hours a day. At the end of this time he developed pain and some discharge in both ears. No sponge-rubber covering for the ears was used at that time. X-ray examination of the mastoid was negative. Examination of the ears was essentially negative although some impairment of hearing was present. The patient was transferred to a municipal hospital for convalescent care.

Examination of the sputum and gastric lavage specimens continued to be negative from January through June, 1942, and intermittently since then to the last examination (September, 1944). For the past two years this patient has been at work part of the time and the rest of the time returned to city institutions, frequently after alcoholic excesses. The

BEFORE 1ST TREATMENT

AFTER 2ND TREATMENT

FIG 6 Case 4 Plamgraphic X-ray films before second course, July 12, 1941, and after four months of equalizing pressure therapy, January 30, 1942

last X-ray films (September, 1944) showed a suspicious highlight where the original cavity had been. His sputum has remained negative. He was discharged from a local hospital after alcoholic excess and is now seeking employment. He has no clinical symptoms of tuberculosis, but X-ray examination (April 6, 1944) indicates that an "apparent cavity is present at the site of the original large cavity." The size of the area is 1 cm. in diameter. There has been progressive decrease in the peribronchial shadows underneath the apparently closed, walled-off cavity (figure 7).

Case 5: Man, age 40 at the time of admission to the Presbyterian Hospital. Eleven years before admission he had bronchopneumonia followed by pleurisy on the right side. He was sent to a sanatorium for nine months. Thoracocentesis yielded yellow fluid. One year before this admission the patient developed fever, weakness and weight loss. During the following eight months he was treated in two hospitals with bed-rest and two thoracocenteses on the left side, one, five and one, four months before this admission. Six months before he had several small hemoptyses. For eight months he had had lower abdominal pain.

He was a thin, middle-aged man, appearing chronically ill. The entire left upper lobe was dull to flat with fine moist râles. The right upper lobe was dull with râles at the extreme apex. At the left base and in the lower axilla dulness and diminished breath sounds were heard. The sedimentation rate was 37 mm. in one hour. The sputum was positive for tubercle bacilli. X-ray examination of the chest showed mottled and streaky shadows in the upper portion of both lung fields. In the right upper lobe the shadows were dense with a radiolucent area of the lower margin. The base of the left lung was obscured by homogeneous shadows and a ribbon-like band of increased density could be seen along the lateral chest wall suggesting a pleural effusion.

After a course of immobilizing pressure therapy for four months, X-ray examination showed clearing of fluid at the left lower lobe and considerable regression of shadows of the left upper lobe. A cavity with fluid level became distinct in the right upper lobe. The sedimentation rate was 7 mm. in one hour on discharge from the hospital, and his weight had increased from 112 to 128 pounds. Six months later his weight was 133 pounds, there was some recurrence of fluid at the left base, with little or no change in the X-ray films.

A second course of equalizing pressure therapy was given during a period of residence from March 4 to June 28, 1941. He was given intravenous promin 4 g. twice daily for one month but this had to be discontinued because of nausea, vomiting and a maculopapular rash. The patient only received intermittent equalizing pressure therapy because of difficulty with the apparatus during this period as well as recurrent complaints such as sinus headache, persisting rash for three weeks and indigestion. Moderate regression of the lesions was manifest on X-ray examination, which continued after transfer to a sanatorium. The sputum was negative during one year at the sanatorium with progressive fibrosis of the tuberculous processes in both lungs. He has been working without symptoms as a hospital technician for almost two years. The accompanying illustration (figure 8) reveals the X-ray picture of the lungs before the first course of therapy, April 9, 1940, and the change after the second course of therapy, July 10, 1941.

Case 6: Man, age 47 years, a candy factory worker who was transferred from a municipal hospital for equalizing pressure chamber treatment. There was no family history of tuberculosis or known tuberculosis contacts.

In 1931 the patient had pneumonia followed, a few weeks later, by right-sided pleurisy.

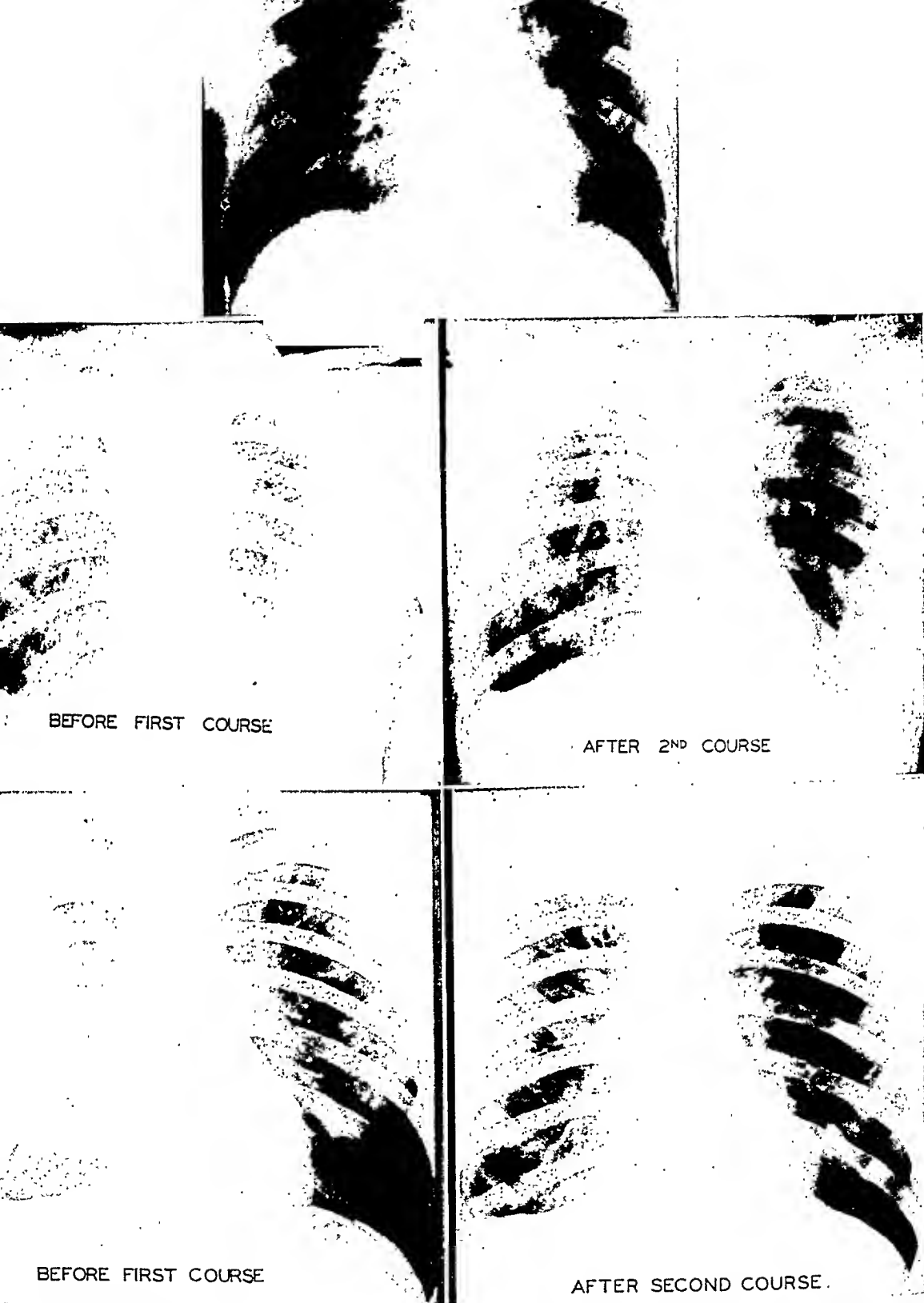


FIG. 7. (Top) Case 4. X-ray film, April 6, 1944, three years after first course of equalizing pressure therapy. This illustration may be compared to figures 5 and 6.

FIG. 8. (Middle) Case 5. X-ray films before first course, April 9, 1940, and after second course, July 10, 1941. Subsequent X-ray films taken through 1944 reveal no change.

FIG. 9. (Bottom) Case 9. X-ray films before first course, December 6, 1942, and after second course, July 7, 1943. Subsequent X-ray films taken one year later show no change.

A chest tap was performed at that time with removal of one liter of fluid. He went to Italy then and returned to the United States in 1940. During the summer of 1941 he began to lose weight, had feelings of malaise, night sweats, and developed chronic cough, productive of about a half cupful of yellowish white sputum, sometimes streaked with blood. He developed wheezes and pleurisy in the right chest in September and, on admission to a municipal hospital the following month, the sputum was found to be positive for acid-fast organisms. He received pneumothorax and five refills before being transferred to a second municipal hospital. On physical examination there, dulness was present over the right lung above T-6, and many fine râles were heard. Fine râles were heard at the base of the left lung. X-ray examination of the chest revealed fibrotic and calcified infiltration at the right apex and a 2 cm. cavity in the upper lobe as well as some collapse by pneumothorax below R-2. No air was present above the apex. The sputum was positive. The sedimentation rate was 46 mm. in one hour.

Collapse was continued but the lesions progressed and thoracoplasty was not considered possible. Another cavity developed above the first one. Fever was continuous and ranged between 99 and 101.5°F. Extrapleural pneumothorax was not attempted. Pneumothorax was discontinued January 28, 1942. The patient was then transferred to the Presbyterian Hospital for immobilizing lung therapy.

Examination revealed a poorly developed and poorly nourished man of 47, chronically and severely ill with marked evidence of weight loss and pale skin. The patient had fits of coughing productive of large amounts of yellowish white sputum. Fremitus was increased on the right side, especially in the upper half of the lung. Dulness was elicited posteriorly about T-4, 5 and 6, an area about 4 by 4 cm., and anteriorly about 4 by 4 cm. about R-2 in the mid-clavicular line. There was bronchial almost cavernous breathing over areas of dulness. Coarse moist râles were heard over these areas, and finer numerous râles were heard throughout the rest of the chest. The right base was flat for about 3 cm. vertically. There was an area of hyperresonance in the axilla above this. Breath sounds were poorly heard in this area. The sounds at the left side were normal; there were a few râles at the base.

The hemoglobin was 80 per cent; red blood cells, 4.62 million; white blood cells, 7,280. The sedimentation rate was 70 mm. in one hour. Many acid-fast organisms were found in unconcentrated sputum. Planigrams of the chest as well as conventional films demonstrated pneumothorax on the right side with a fluid level at the bottom of the pneumothorax cavity. There was not very much fluid. There were at least three large cavities in the upper half of the right lung field. There were also numerous calcium shadows along the mediastinal border and scattered throughout the right upper lung field. The cavities had rather thick walls and contained no fluid. The left lung field was clear.

The patient was started on immobilizing lung therapy, the duration being gradually increased to twelve hours daily during the first week. Inhalation of the nebulized spray of promin was started three times daily, a total of 4 g. of the solution being given. At the end of one month persistent nausea developed and the promin was discontinued for two weeks. During this time the temperature which had previously varied from 99 to 101.5°F. decreased to 99 to 100°F., and he gained 10 pounds.

X-ray examination of the lungs showed a definite decrease in the size of the lower two cavities in three months, but further improvement did not take place. After four months' treatment he was returned to a municipal hospital, as unimproved.

Case 7: The history of this patient was fully described previously as case 4 in the first report (6) and will therefore be very briefly summarized here. A colored man, aged 45

years, entered a municipal hospital after one year of symptoms of weakness, weight loss and cough. During three months at this institution his temperature gradually increased from 100 to 104.5°F. The tuberculous process had extended progressively throughout both lungs with the appearance of large bilateral cavities and wide-spread surrounding infiltration. He was treated in the immobilizing pressure chamber mainly to determine the effect on fever, which decreased to a range of 100 to 101°F.; there was some regression of the lesions by X-ray at the end of one month. He subsequently developed a tuberculous pneumonia, was treated in the oxygen chamber, returned home for several months and finally entered a municipal hospital where he ultimately died.

Case 8: Male, aged 19, of Italian descent. Present illness began with a cough four years prior to admission. The diagnosis was made three months after onset of symptoms when X-ray examination showed a cavity in the right lung as well as a lesion on the left. Soon after, a pneumothorax was instituted on the right side and a pneumonolysis was performed. Empyema developed in that side and a tube was inserted into the empyema cavity for six months. A cavity then developed in the left lung, pneumothorax was instituted for six months and then abandoned. He was at home for part of the time thereafter and, for the year preceding admission to this hospital, was at a municipal tuberculosis institution. No improvement took place on bed-rest.

On admission to this hospital he was found to be a patient of moderately good nutrition, almost afebrile; weight 160 pounds. Stereoscopic and planigraphic X-ray examinations of the chest showed an irregular infiltration involving the upper one-third to the upper half of both lung fields. Cavities, 2.5 cm. in width, were noted in both infra-clavicular regions. The sputum was positive for acid-fast organisms.

After one month of immobilizing lung therapy, X-ray examination revealed a definite diminution in the size of the large cavity on the right side. However, at the end of four months no further improvement took place and a second course of four months' therapy was instituted. At the end of this time there was a marked diminution in the size of the cavity in the right lung, but on the left side there was evidence of an increase in the size of a cavity at the level of the second rib, from 1 to 1.5 cm. in diameter.

The patient was transferred to a municipal hospital where a thoracoplasty was performed on the left side, and the patient was later sent to another hospital; his general condition was fairly good.

In this patient complete immobilization of the lungs was not continuously achieved. He persisted in a tendency to fall asleep in the chamber, during which time spontaneous voluntary respiration took place. In addition, the gauge which represented the differential pressure was out of order for a considerable period of time and unfortunately excessive pressure on the head end was maintained until a water manometer indicator was substituted. Despite the decrease in the size of the cavity on the right side this patient is considered as not significantly improved.

Case 9: Man, age 20 years. Two years and two months before admission to this hospital an X-ray examination at the draft board showed pulmonary tuberculosis and positive sputum was found. He had had a slight cough with fatigue and weight loss of 10 pounds previously. When he entered a city institution he was found to have fairly advanced disease. The X-ray film showed a mixed infiltration in the upper one-third of the right side with a 2 cm. cavity. The pleura was thickened and there was evidence of free fluid in the right axillary region. A right pneumothorax was attempted but was not successful. After one month the patient was transferred for immobilizing lung therapy. He

at first ran a fever up to 99.6°F. and expectorated about one-quarter of a cupful daily. Cough and expectoration almost entirely stopped after two weeks of treatment with a 10 pound gain in weight. The patient was treated for four months at which time the cavity had disappeared. He returned to the city institution where recurrence of pleural fluid was found. About 300 cc. of slightly cloudy fluid was aspirated and was positive for acid-fast bacilli on direct smear. He was then readmitted to this hospital for a further course of treatment. At the end of four months there was still some fluid in the right pleural space but no evidence of cavity could be found. The accompanying illustration (figure 9) reveals the X-ray appearance of the lungs before the first course, December 6, 1942, and after the second course of therapy, July 7, 1943. He was sent away for convalescent care. After seven months he was discharged from a municipal sanatorium as being free from active disease. The sputum was consistently negative; there was no evidence of cavity; the fluid in the left pleural cavity was absent. For one month the patient was ambulatory at home and for the past six months he has been at work as a technician in the hospital part of the time and at home the rest of the day.

This patient represents a less advanced type of disease than the other cases in this series. Two courses of therapy appeared to result in final and complete arrest of the tuberculous process with disappearance of the cavity and pleural fluid and ultimate return to work with somewhat restricted activity.

Case 10: A woman, aged 27. Father died of pulmonary tuberculosis. Six years prior to present admission patient developed increasing fatigue and cough. Six months later an X-ray examination showed far advanced tuberculosis with two cavities in the right upper lobe and one larger cavity in the left upper lobe. After bed-rest pneumothorax was instituted, first on one side then on the other, followed by bed-rest for seven months. After three years of somewhat restricted activity the lungs were allowed to expand and the patient went back to work. Seven months before admission the patient had a small hemorrhage and X-ray examination then showed return of the cavity on the right side and shortly after on the left side also. A bilateral thoracoplasty was advised. From then on she was at bed-rest until transfer to the Presbyterian Hospital.

Examination showed a well nourished young woman; crepitant râles over both upper lobes, anteriorly and posteriorly. X-ray examination showed a rather extensive fibrosis in both apices. There were two cavities, 5 cm. in width, in each upper lung field and several smaller thin-walled cavities on the right side. There was little reaction around them. The sputum consistently showed many acid-fast bacilli.

After three and one-half months of immobilizing lung therapy the original large cavity in the left side was no longer visible, either in stereographic or planigraphic X-ray films. Three weeks later the patient was allowed to leave the city for one day, and subsequent planigraphic X-ray films suggested that the walls of the cavity had separated. Three weeks later a definite cavity on the left side was again observed.

Immobilizing lung therapy was stopped for one month and during this time the patient was allowed to leave the hospital for a three-week period. When she returned the cavities in both the right and left upper lobes were considerably larger. Immobilizing lung therapy was instituted for two and one-half months.

During the first admission the patient ran a slight fever, 99 to 100°F., for the first month. Her temperature then became normal, the range being smaller, 98.6 to 99°F. Her weight remained constant at 131 pounds. X-ray examination showed disappearance of the cavity in the left lung after the first course of immobilizing lung therapy, with recurrence after premature activity.

A crushing of the phrenic nerve had been instituted on the left side of this patient before the second course in an attempt to determine whether a decreased movement of the diaphragm would decrease the time required for collapse of cavity which is obtained by immobilizing lung therapy. Since lung rest is provided the majority of the time during the day, gradual collapse of the cavity takes place as the result of day-time arrest of lung movement. It is to be expected that movement of the lungs in the latter part of the evening and at night to some extent retards the collapse of cavity which takes place during the day. The possibility presented itself that decreasing the diaphragmatic movement on that side might be of value not only during the course of immobilizing lung therapy, but when the treatment itself had ended. In this patient the fact that the cavity reopened after three years of pneumothorax and again after the first course of immobilizing lung therapy following short exposure to limited activity suggested that complete closure of the cavity with healing with fibrous tissue would be difficult to obtain. At the end of two months in the chamber the infiltration beneath the cavity on the left had slightly increased although the cavity was 30 per cent smaller. The second course of treatment was stopped, and the patient is soon to have bilateral thoracoplasty.

DISCUSSION

The results of the type of lung rest provided by immobilizing pressure therapy in advanced pulmonary tuberculosis suggest that this procedure has decisive therapeutic value not only in aiding the resolution of exudative lesions but in initiating the collapse of tuberculous cavities (table 1). All the patients in this series were considered to have had either too advanced disease or disease unsuitable for thoracoplasty; bilateral thoracoplasty had been advised in case 10.

The first patient had one course of four months' treatment, beginning May 6, 1938. Marked clinical improvement took place with progressive clearing of advanced bilateral disease. His follow-up has shown consistently negative sputum tests. Except for a three-month period of bed-rest he has been well and working for about five years.

The second patient had shown larger cavities in both lungs and received in all three courses of immobilizing lung therapy, in each of which a definite collapse of cavity took place finally with clearing of all infiltrative lesions, persistently negative concentrated sputum and absence of expectoration and cough. He has been clinically well and at work for approximately three years. After the third course he was given six weeks of treatment with the nebulized spray of promin. Whether inhalation of promin spray had an effect in final contraction of the small residual cavity in the left lung cannot be decided.

The third patient with bilateral advanced pulmonary tuberculosis had one course of four months' treatment which was followed by clearing of infiltrative lesions in both lungs and a temporarily negative sputum. A partial left pneumothorax was maintained for about one year. Since it was discontinued repeated examinations of concentrated sputum were consistently negative for over one year.

The fourth patient with advanced bilateral tuberculosis showed moderate improvement in each of two courses of immobilizing lung therapy and, after one subsequent year of convalescent care in a sanatorium, was discharged as arrested. He has been working and well for more than two years.

The fifth patient had a large cavity in the left lung which collapsed in the first course of treatment, reappeared at convalescent bed-rest and again collapsed on a second course of treatment. This patient has had continued negative sputum tests. He is free from clinical symptoms. During the last course of immobilizing lung therapy he received inhalation of nebulized spray of promin. Following this a dense shadow replaced the region where the cavity was formerly seen. Whether the promin was in part responsible for contraction of the cavity cannot be definitely stated. He has frequently entered municipal institutions, generally after alcoholic excesses. For part of the past two years he has worked. At present he is seeking employment. His last sputum tests were negative. An apparent cavity (1 cm.) at the original site appears to have recurred, although much smaller than the original lesion.

The sixth patient had shown advancing tuberculosis at bed-rest with progressive loss of weight, fever and the final appearance of three large cavities in the right lung. Treatment in the equalizing pressure chamber for the first month was followed by a gain of 10 pounds in weight and the disappearance of most of the febrile reaction. Inhalation of the nebulized spray of promin was given during this period. Interruption of immobilizing lung therapy was followed by recurrence of fever, even though inhalation of promin solution was continued. Resumption of immobilizing lung treatment was followed by almost complete disappearance of fever in each of three separate periods of approximately one month each. There was slight contraction of the three large cavities in the right lung. The patient was considered unimproved.

The results of the inhalation of the nebulized spray of promin are reported more from the point of view of suggesting a method of possible clinical value rather than as a demonstration of therapeutic advantage in these cases.

The seventh case was previously reported as a man who had developed bilateral extensive disease with a temperature of 104.5°F. on previous bed-rest in a municipal institution. During immobilizing pressure therapy his temperature decreased and he was temporarily improved, but later the onset of tuberculous pneumonia was followed by a spontaneous pneumothorax. He was discharged home, ultimately returned to a municipal hospital and finally died.

The eighth case was that of a man who had two courses of immobilizing pressure treatment for advanced bilateral pulmonary tuberculosis. In this patient the improvement was slight and he was ultimately returned to the municipal institution. A thoracoplasty on the left side is scheduled for him at this writing. He is classified as unimproved.

The ninth case is that of a man who after two courses of immobilizing pressure treatment became clinically well, the cavity disappeared and the sputum has been negative for over one year. He is now at work for a period of three months.

The tenth patient was advised to have bilateral thoracoplasty. The presence of large cavities at the top of both lungs which reappeared following termination of pneumothorax appeared to offer no other therapeutic possibility. During the first three months of immobilizing pressure therapy, the cavity collapsed and became invisible on X-ray films. This cavity reappeared on slight activity and a second course of immobilizing pressure therapy is being carried out at this

time. In this patient a combination of crushing of the phrenic nerve and local lung rest has been instituted in the hope that activity following the collapse of the cavity will not cause a reopening of the cavity.

The provision of lung rest makes possible a decrease in the elastic tension of the lung, since cessation of movement of the lungs takes place at the conclusion of a normal expiration. Furthermore, cessation of lung movement diminishes the diffusion of toxins from the tuberculous lesion. The state of relaxation which takes place during cessation of voluntary breathing not only is helpful in adding to local lung rest a type of body rest which is not possible under circumstances of normal breathing, but also provides mental relaxation. It is noteworthy that patients who have a keen desire to smoke cigarettes do not miss them as much during the period when they are in the chamber as they do during ordinary bed-rest.

In appraising the results of 2 patients in whom improvement did not occur, the *continuousness* of arrest of lung movement was probably a factor. In one, the frequency with which he was found asleep suggested that absence of lung movement did not take place sufficiently in his case. In patients who fall asleep during treatment there is frequently observed recurrent voluntary breathing.³

In cases in which cavities are adherent to the chest wall over a wide area, collapse of the cavity may be prevented. It is also conceivable that a large cavity with a very small bronchial opening may suffer some expansion and contraction in its size if there is not a sufficiently free inlet and outlet of air through the respiratory passageway connected to the cavity. It may also be pointed out that mistakes have been made in regulating the differential pressure applied to the head and to the body. A water manometer is a safer guide to the maintenance of the differential pressure than a guage, since the latter was found to have become inaccurate and, for a considerable period of time, led to an unusually high pressure being applied at the head end (case 8).

During the use of immobilizing pressure therapy during the past six years, the technique of regulating this method of treatment has become simpler and better understood. It is of considerable importance to observe the chest wall for signs of movement while the differential pressure of 5 cm. of water is being tried. In some patients a differential of as low as 3.5 to 4 cm. may be all that is neces-

³ This may be with the cycle of the machine or against it. Thus, during the positive pressure wave, air is entering the lung. The patient may inspire during this cycle or he may inspire during the negative pressure wave. In the second instance he would be withdrawing air from the lung by expansion of the chest at the same time that air was being distributed to the lung by compression. During ordinary inspiration enlargement of the chest provides for an inlet of approximately 500 cc. of air into the lungs. If an inspiration were to take place during the positive pressure cycle the inlet of air would be facilitated by compression of the air within the chamber. However, if inspiration takes place during the phase of negative pressure the inlet of air into the lungs produced by inspiratory enlargement of the chest would be to a variable extent counteracted by expansion of the air within the chamber under the conditions of negative pressure which would tend to force air out of the lungs. In either event, when patients are asleep breathing is apt to take place, as was often observed in this patient (case 8).

sary to prevent excursion of the chest wall whereas, in others, pressure of 6 to 7 cm. of water may be required. The fact that considerable difficulty was experienced in determining the right pressure for case 8 may have been partly responsible for the failure to achieve a good result in his case.

The technique of applying this treatment is simple although it does require observation of the patient every two or three days to be sure that the differential pressure is correct, that the patient is able to dispense with voluntary breathing and that the chest wall is motionless. It is important to instruct the patient not to fall asleep and to make sure that this does not take place.

The third case that did not get better had bilateral very extensive disease with large cavities, a rapidly progressive course with a temperature of 104.5°F. every evening. In this case the almost terminal state of the patient was such as to prevent any actual hope for cure. Not only was there wide-spread caseous tuberculosis with large cavities, but the patient had on previous bed-rest of three months' duration shown a gradual increase in temperature from 100°F. to 104.5°F. The treatment was instituted largely to show the effect of local lung rest on toxemia and temperature. At first the patient had to be carried into the chamber and later his clinical improvement was revealed by his ability to walk into the chamber and by a temperature which had decreased to 101°F. The subsequent development of tuberculous pneumonia prevented further trial of the apparatus but this case did nevertheless reveal signs of diminution of toxemia which local lung rest produced.

In case 6 the three cavities were of large size, occupying the upper and middle lung field. It may be that they were to a large extent adherent to the chest wall and perhaps the bronchial passageway leading to the cavity was not sufficiently large in relation to the volume of the cavity to provide a free entrance and exit of air during the positive and negative phase. Although an initial improvement appeared to be manifested by a decrease in the size of the lower cavity, no permanent betterment took place.

It is naturally not to be expected that all cases of pulmonary tuberculosis, especially those with as advanced disease as reported in this series, should manifest complete and permanent recovery. The results obtained were far better than was expected, since recovery took place in cases that had shown no response to routine measures. The conclusion that this type of local lung rest aids the process of healing and tends to result in collapse of cavities seems justified. The recurrence of cavity which necessitated a second course of treatment, and in one case a third course of treatment, suggests that the period of therapy was too short in some of these cases. Cavity walls may coalesce without actual healing taking place and increased activity may then result in opening of the cavity. Although a second course of treatment resulted in closure of the cavity in those cases in which it was tried, the likelihood is present that in some instances the cavity may only be temporarily closed and may not remain so unless actual disappearance of the walls and replacement by fibrous tissue occur.

A few remarks seem indicated concerning the practical aspects of this treat-

ment. The chamber itself is of relatively simple construction and should not present any difficulties in operation to a person with a short period of training in its use. Since it employs only outside air there is no expense beyond that of the electric current used. The initial cost of the chamber is not great, especially when considered in terms of the actual long term cost of treatment for patients with pulmonary tuberculosis. From the standpoint of the patient himself, we have encountered no resistance whatsoever. The possible fear that the patient may have of claustrophobia by being placed in a chamber has seemed to be largely in the mind of the physician who was unused to this type of therapy. In every instance the patient himself liked the treatment and when it was possible for him to take a second course he was anxious to have the opportunity to do so. There was, therefore, no psychic hurdle to overcome in patients who undertook this type of lung rest and body rest. Furthermore, the mental relaxation which takes place when voluntary respiration has been abandoned makes possible a cheerful attitude during the course of therapy. At times patients get fed up with the chamber for short periods, but in all instances there has been a willingness to return to it in a few days. The treatment has never been terminated at the wish of the patient, but always when it was decided that the time had arrived to try convalescent care. The development of an acute otitis media in one patient during a two-week period may have been due to the variations in chamber pressure. Wearing sponge-rubber coverings to the ears minimizes these pressure effects. The patients who had two and three courses showed no injurious consequences in respect to ear function.

SUMMARY AND CONCLUSIONS

The effect of immobilizing both lungs by residence in an equalizing pressure chamber is described in 10 patients with advanced pulmonary tuberculosis. In 4 of these patients either little improvement took place or the benefit obtained was temporary and did not influence the course of the disease. In the remaining 6 patients significant improvement was observed. In one patient collapse of a large cavity took place in four months, recurred on slight activity and was closed again in a second course with fibrous tissue scar formation. Subsequently, a cavity, 1 cm. in diameter, was seen by X-ray at the original site. Repeated individual and concentrated sputum tests have been negative for two years.

The remaining 5 patients became clinically well and were discharged as able to work. Four of them are known to be at work, free from evidence of illness, with negative sputa, and either without signs of tuberculosis by X-ray or with fibrotic arrest of the disease. One patient has been working almost five years, 2 patients between two and three years, one was lost sight of after a follow-up of over one year. The fifth patient has been working part of the time for six months only, although he has been clinically well one and one-half years.

Of the 5 patients who have been discharged as able to work, 2 had one course of immobilizing lung therapy of four months' duration, 2 others had two courses of treatment and the fifth patient had three courses of treatment. The sixth

patient who was significantly improved, but who is not well, had two courses of treatment.

A transportable equalizing pressure chamber has been developed to provide local lung rest, which is relatively simple in operation. Although the method has been applied to advanced cases, it may be employed in patients who have less extensive disease.

SUMARIO Y CONCLUSIONES

Descríbese el efecto producido por la inmovilización de ambos pulmones en 10 enfermos de tuberculosis pulmonar avanzada, mediante la permanencia en una cámara igualadora de la presión. En cuatro de ellos, o se observó poca mejoría, o el beneficio obtenido fué temporal sin que se afectara la evolución de la dolencia. En los otros seis, notóse mejoría significativa. En un enfermo tuvo lugar en cuatro meses el aplastamiento de una caverna grande, que recurrió tras una actividad ligera y se cerró nuevamente con otra serie de tratamiento, con formación de tejido fibroso de cicatrización. Los rayos X revelaron después una caverna de 1 cc de diámetro en el sitio primitivo. Las repetidas pruebas en el individuo y en el esputo concentrado han resultado negativas por dos años.

Los otros cinco pacientes se repusieron clínicamente y fueron dados de alta con capacidad para el trabajo. De cuatro se sabe que continúan trabajando sin signos de enfermedad, con esputos negativos, y bien sin signos de tuberculosis a los rayos X o con estacionamiento fibroso del mal. Un enfermo ha trabajado casi cinco años, dos entre dos y tres años y uno se ha perdido de vista después de una observación de más de un año. El quinto enfermo ha estado trabajando parte del tiempo solamente durante seis meses, aunque se ha encontrado clínicamente bien por espacio de años y medio.

De los cinco enfermos dados de alta como capaces para trabajar, dos recibieron una serie de terapéutica inmovilizadora del pulmón que duró cuatro meses, otros dos, dos series, y cinco tres series. El sexto enfermo que mejoró notablemente, pero que no se halla bien, recibió dos series.

Se ha elaborado una cámara portátil de igualación de la presión que suministra descanso local al pulmón y cuyo funcionamiento es relativamente sencillo. Aunque la técnica ha sido aplicada hasta ahora sólo a casos avanzados, también puede ser utilizada en enfermos en que la enfermedad se ha difundido menos.

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BRONCHOGRAPHY IN PULMONARY TUBERCULOSIS¹

VI. Thoracoplasty

Part 1

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In a previous paper (no. IV) we endeavored to depict the geography of pulmonary tuberculosis by means of bronchograms. We showed that even in the earliest stage of the disease there is block of the bronchial tree at some point and bronchiectasis or cavitation arises as a result of this obstruction. We then demonstrated the effect of artificial pneumothorax on such changed tissue. In this paper we discuss the therapy in cases of "failed pneumothorax."

In a recent publication (1) we stated, under the heading of Thoracoplasty, "This is collapse therapy with a vengeance. One always feels that a thoracoplasty to knock out a tubercle bacillus is like using a sixteen pound hammer to kill a flea on a cat. The flea is often killed, but so is the cat." Thoracoplasty aims at collapsing cavities and diseased areas of lungs. We wonder how often it succeeds and, when it does, how much healthy lung has to be sacrificed to this great god collapse. If there is one thing we have learned from a study of thousands of bronchograms in pulmonary tuberculosis it is that when a lung is damaged beyond a certain minimal degree the damage is irreparable.

As far as we can ascertain, the decision to do a thoracoplasty is usually based on reading a conventional X-ray plate, on physical signs, on a general evaluation of the patient, on a persistently positive sputum and on the failure of other methods of treatment—mostly on the failure of other treatment. This supreme achievement of the art of the thoracic surgeon is perhaps an admission of failure, and this attitude of despair goes even further to-day because, when all the stages are over, an eventual pneumonectomy is often done because the patient still has copious sputum.

We have learned that the recent cavity which will not respond to artificial pneumothorax, especially a cavity in the upper part of the lung, is perhaps the ideal indication for this operation. The results in any other stage of tuberculosis cannot be predicted. Some cases emerge with a negative sputum, some with a positive, but one cannot say beforehand which case will attain a negative sputum and which will not. It was this very lack of the ability to predict the outcome of the operation that led us to study the bronchial tree in cases submitted for thoracoplasty and to study its reaction to each stage of the operation.

We learned that no case is a simple proposition of cavities to be closed, but primarily a bronchiectasis with cavitation; that this curse of bronchial block dogs all cases of pulmonary tuberculosis and leaves a trail of devastation. We realized that tuberculous bronchiectasis and cavitation are pathologically similar to ordinary bronchiectasis and lung abscess. Yet, although thoraco-

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plasty has been abandoned as a treatment for the latter forms of lung damage, it is used almost indiscriminately in tuberculosis.

We found that after operation cavities may be closed, but bronchiectasis remains in every case. Even if a complete and satisfactory operation is done and all cavity walls approximated, there is a residual bronchiectasis which may or may not give rise to positive sputum. We therefore came to the conclusion that thoracoplasty is a hit-or-miss affair and that, in fact, the end-result is not due to the skill of the operator or the prognostic ability of the physician, but to some factor beyond our knowledge or control.

Very often the spread of disease is prevented in the lung originally affected by destroying all the functioning tissue. A simple accident of in-coughing can spread the disease to the opposite lung and sabotage all our prolonged effort. We discovered also, to our amazement, that very often our sincere, but apparently misguided efforts led to further bronchiectasis which developed in a quiet, insidious and unheralded way.

The realization that we have no firm ground on which to base a prognosis in our thoracoplasty cases has led us to attempt other methods of treating tuberculous cavitation and bronchiectasis. For some time we have been experimenting with repeated instillation into the bronchi of suspensions of various sulphonamides in lipiodol. We are able to concentrate as much as 3 g. of sulphonamide powder in a few dilated bronchi—an enormous amount compared with the quantity which would reach the bronchi after oral administration. So far some cases have benefited sufficiently at least to encourage us to continue, but a long time must elapse before we can venture an opinion as to the efficacy of the treatment. It may be but another delusion beckoning the weary medical pilgrim who seeks a "*therapia sterilans magna*."

In the series of cases which we present we deal, first, with the successful cases and, second, the unsuccessful. By success we mean the achievement of a negative sputum and by failure a persistently positive sputum. We discuss each case and ask for indulgence in our perplexity. As all were left with a bronchiectasis, why did some end in apparent cure and others not? Was it due to the surgical manipulation or luck?

It will be argued, of course, that in some cases the persistent positive sputum may arise from tracheobronchial lesions which can be revealed by bronchoscopy. We have already demonstrated in this series of papers, however, that all old-standing tuberculous lesions are bronchiectatic. In other words, they all have bronchial tuberculosis, although in only a few are the bronchi affected within the vision of the bronchoscope.

In a case with a single, relatively early apical cavity, which is the most suitable type for thoracoplasty, there may be no demonstrable bronchiectasis. In all other cases there is tuberculous bronchiectasis present before thoracoplasty, and the bronchiectasis remains unchanged after the operation. It is this fact that makes it important to find some more logical form of therapy than thoracoplasty.

CASE REPORTS

Group I. The Successful Cases

Case 1: C.389, Indian female, aged twenty-three years. About a year before admission she spat up some blood and was advised to go up country for a holiday. Six months after this she again coughed up some blood and has had a cough with a little sputum since that occurrence. She is a healthy looking Indian female. Temperature is between 97 and 99.2°F.; pulse 84 to 96. Sputum contains tubercle bacilli. The physical signs are prolonged expiration and some crepitations at the right upper lobe.

An X-ray film of her chest (figure 1) shows a cavity approximately 2 x 2 inches at the right apex and some scattered areas of infiltration in the right infraclavicular region below the cavity.

A bronchogram (figure 2) (patient lying down) shows a kidney-shaped cavity with its draining bronchus, blocked bronchioles in the area of infiltration and an absent alveolar pattern in this area. The rest of the lung has a normal bronchial pattern. A well marked fluid level was evident with the patient in the erect position.

A right artificial pneumothorax was attempted without success; so a first-stage thoracoplasty was performed.

A bronchogram (figure 3) shows the result of the operation. The cavity walls have been approximated and there is left a residual, but minor degree of bronchiectasis of the upper lobe.

This case is one with a thin-walled apical cavity with some surrounding inflammation. It should be noted that the shape and size of a cavity, as revealed by bronchography, are never the same as in conventional radiography. This bronchographic shape never varies in successive bronchograms and is probably a true picture of the interior of the cavity. The much larger rounded area seen in a conventional radiograph is probably due to inflammatory change with its nonaerated tissue round the cavity. The residual bronchiectasis after thoracoplasty in such a comparatively early case should be noted carefully.

Case 2: E.470, European male, aged thirty-four years. Fourteen years ago this patient had a right pleural effusion which kept him in bed for six weeks. Nine years later he had a left pleural effusion and again had six weeks in bed. Three years ago he coughed up a little blood on one occasion. He has had a positive sputum for the last two years. He is a fit, bronzed, healthy looking European. Temperature and pulse are normal. Sputum contains tubercle bacilli. The only physical signs are increased vocal resonance over the right apex.

An X-ray film (figure 4) shows clouding of the right apex and infraclavicular region and clouding of the left apex.

A bronchogram (figure 5) shows bronchiectasis of the right upper lobe, the bronchi terminating in cavities. The rest of the bronchial tree shows normal filling.

A right artificial pneumothorax was attempted but was not successful. A first-stage thoracoplasty was done.

A bronchogram at this stage (figure 6) shows that the bronchiectasis remains unchanged, but the cavity walls have approximated.

Following this operation the patient's sputum became negative and has remained negative for two years, although the patient has followed the strenuous occupation of a sur-

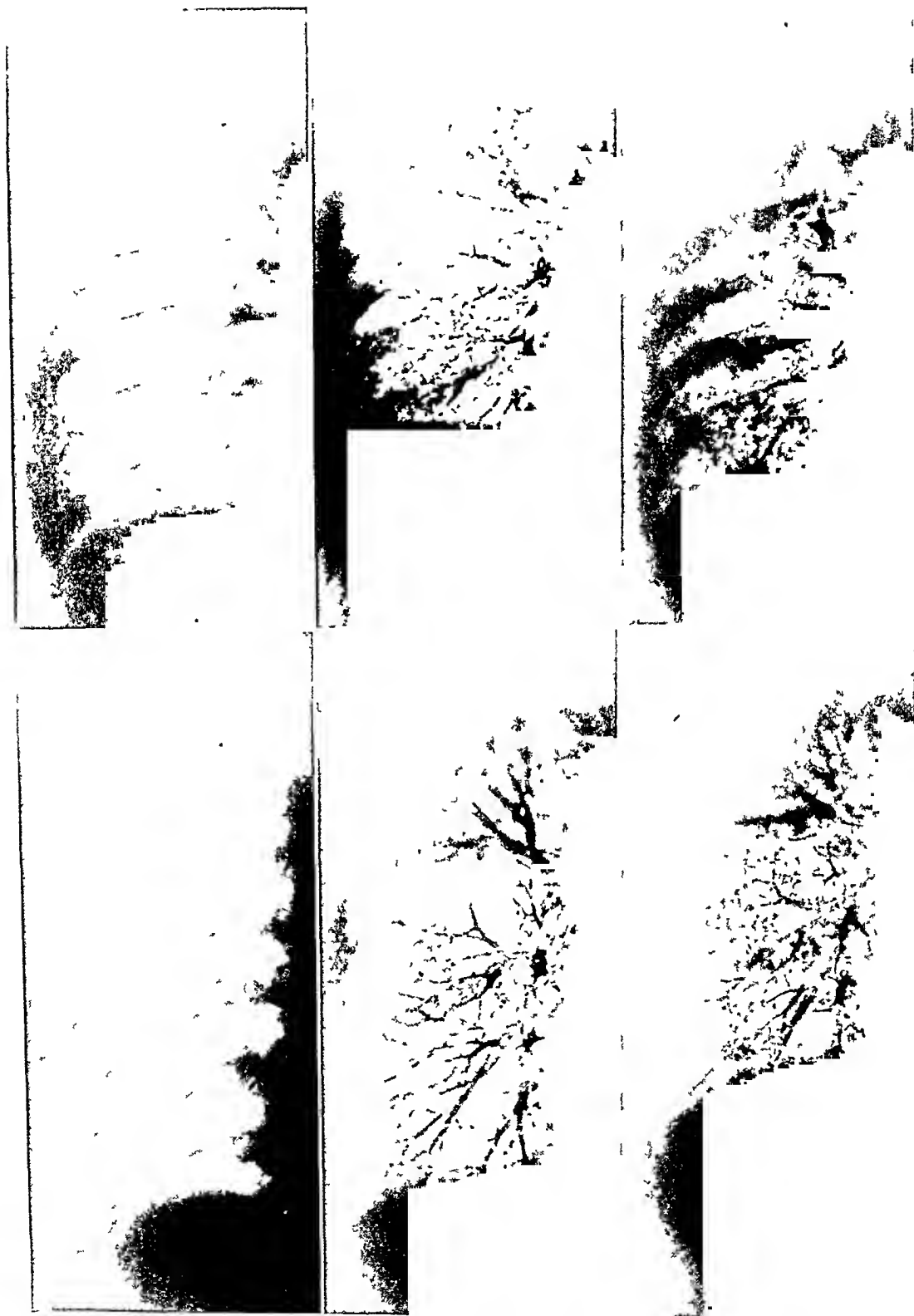


FIG 1 Upper left; FIG 2 Upper centre, FIG 3. Upper right, FIG 4 Lower left; FIG 5 Lower centre, FIG 6 Lower right

veyor. This case again shows the residual bronchiectasis which would not disappear even after further stages of the operation. We do not know why the sputum became negative unless the tubercle bacillus was flourishing in the cavity walls only.

Case 3: E.371, European female, aged twenty-three years. Four years before admission patient had a cough and brought up sputum. She had a right artificial pneumothorax induced and this was continued for ten months and then abandoned. She felt quite well for three and a half years when he began to cough and produce sputum again. She is very fit looking and plump. Temperature and pulse are normal. Sputum contains tubercle bacilli. The physical signs are dulness and bronchial breathing with crepitations at the right upper lobe.

An X-ray film (figure 7) shows a "black-out" of the right upper lobe with upward pull of the interlobar septum and deviation of the trachea to the right.

A bronchogram (figure 8) shows extensive bronchiectasis of the right upper lobe and normal alveolar filling of the lower lobe.

A first-stage thoracoplasty was performed and the sputum remained positive.

Figure 9 is a bronchogram after the first stage operation, showing that the bronchiectasis is still present and that the lower lobe bronchial tree no longer has a normal filling.

A second stage was done. Figure 10 is a bronchogram after this stage and shows the persistent bronchiectasis of the upper lobe and the crowding and dilatation of the bronchi of the lower lobe.

The sputum still remained positive and a third stage was duly carried out. A bronchogram (figure 11) shows the completed operation with residual bronchiectasis in all the bronchi in both upper and lower lobes.

The patient's sputum after this final operation became negative and has remained so for a year.

This case is most instructive. The bronchograms depict how, in order to collapse an upper lobe lesion, it became necessary to destroy all the functioning lung on the right side. The end-result was a formidable bronchiectasis much greater in extent than the original lesion, but the sputum became negative. Why?

Case 4: C.1, colored male, aged forty-one years. Two years before admission he developed fever and was admitted to a hospital where tuberculosis was diagnosed. He remained some months in a sanatorium and was well until admission to King George V Hospital, when he had sputum which was tinged with blood. He is a fit looking colored male. Temperature and pulse are normal. Sputum contains tubercle bacilli. The physical signs are dulness and crepitations over the left upper lobe, whispering pectoriloquy in the left infraclavicular region and crepitations over the whole of the rest of the left lung. There are a few crepitations over the right apex.

An X-ray film shows a "black-out" of the whole of the left lung. A bronchogram (figure 12) shows that the whole of the left lung is excavated and that there is a very thick pleura on this side.

A thoracoplasty was carried out in stages and figure 13 shows the result after the last stage. The end-result is bronchiectasis and basal cavitation, admittedly not so extensive as at the start.

Yet, after the final stage, the patient had a negative sputum and it remained negative for two years before he was killed in a motor accident.

Case 5: E.62, European male, aged thirty-five years. Twelve years ago, while having a routine examination for insurance, he was told he had tuberculosis. He then spent

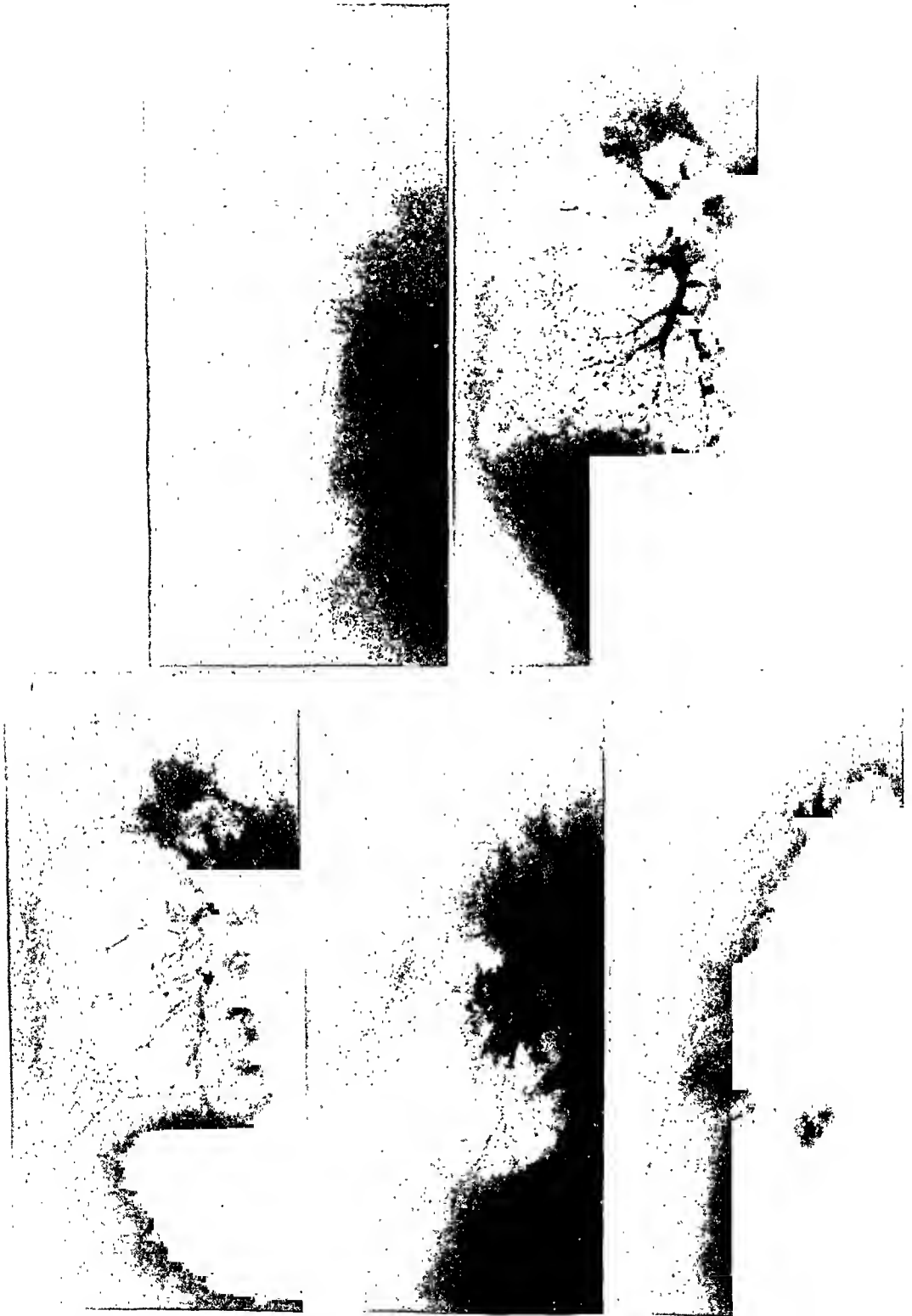


FIG. 7. Upper left; FIG. 8. Upper right; FIG. 9. Lower left; FIG. 10. Lower centre; FIG. 11. Lower right.

several years in and out of sanatoria until eventually, a few years before admission, he had a thoracoplasty done in several stages. He felt well after this but his sputum has been consistently positive. His temperature and pulse are normal. Sputum contains tubercle bacilli. There is a complete thoracoplasty on the right and scoliosis. There is no evidence of disease on the left side.

X-ray examination shows a thoracoplasty on the right but the first rib is still present. It was decided to remove the first rib and this was done shortly after admission.

A bronchogram shows that the end-result of the operation is a bronchiectasis throughout the whole lung. Yet the patient's sputum became negative after the operation (removal of the first rib) and has remained negative for the last three years.



FIG. 12. Left; FIG. 13. Right

Group IA

This subgroup contains 4 cases in which, as in the previous ones, the sputum became negative after thoracoplasty. These 4 patients, however, had intra-bronchial instillation of sulphonamide in lipiodol on several occasions both before and after operation. We do not know whether this treatment assisted in bringing about a negative sputum, but it is at least a reasonable possibility.

Case 6: E.564, European male, aged thirty-two years. He has coughed for six months—a morning cough with a little sputum. He felt perfectly fit otherwise until six weeks ago when he developed an acute appendicitis. Following the operation it was noticed that he was coughing and had fever. His chest was X-rayed and pulmonary tuberculosis

diagnosed. He is a very ill looking man. Temperature is between 98.8 and 100°F.; pulse 80 to 120. Sputum contains tubercle bacilli. Physical signs are wasting and diminished movement over the right upper lobe with increased vocal resonance and bronchial breathing in this area.

An X-ray film showed extensive bilateral pulmonary tuberculosis and he was treated by bed-rest and gradual exercises for fourteen months, when his sputum became negative and an X-ray film showed what appeared to be healed disease at the right apex.

He was discharged and a few days later, while taking a cross country journey in a bumpy bus, he had an hemoptysis. He was readmitted to the hospital and his sputum was again found to contain tubercle bacilli.

The X-ray film on readmission showed a ring shadow just below the right clavicle at the periphery, about one-half inch in diameter and the right apex was obscured.

A bronchogram showed bronchiectasis of the right upper lobe and normal alveolar filling of the rest of the lung, except at the extreme base near the mediastinum where there was some terminal bronchiectasis.

A first-stage thoracoplasty was performed. There was still a minor degree of bronchiectasis at the right apex and in the terminal bronchi at the base near the mediastinum.

Following the operation the patient's sputum became negative and has remained so for the last six months.

Case 7: E.639, European female, aged thirty-six years. The onset of her disease was about eight years ago with malaise, cough and pain in the left shoulder. She was not X-rayed for two years after the onset. When tuberculosis was diagnosed she was sent to a sanatorium for spells of six months and had a left artificial pneumothorax attempted but this was not successful. She then had a left phrenic avulsion. She is fit looking. Her temperature and pulse are normal. Sputum contains tubercle bacilli. The physical signs are dulness with whispering pectoriloquy and scattered crepitations over the left upper lobe.

An X-ray film shows fibroid phthisis of the left upper lobe. A bronchogram (figure 14) shows extensive bronchiectasis of the left upper lobe with upward pull of the left main bronchus.

A first-stage thoracoplasty was performed and a bronchogram shows the result (figure 15). The bronchiectasis still remains although there has been a fair amount of collapse of the bronchiectatic bronchi upon themselves.

After the operation the patient's sputum was positive on one occasion. Following the intrabronchial instillation of sulphonamide suspension in lipiodol, in order to obtain figure 15, her sputum became negative and has remained so.

Case 8: E.500, European male, aged twenty-eight years. The onset of his illness was eight years ago when he had pleurisy. He was in bed for three weeks only. A year later he had cough and was X-rayed and pulmonary tuberculosis was diagnosed. He was in a hospital and a sanatorium for a year after this. He then returned to work and, although he had a slight morning cough, he never bothered about this. Three months before admission he fell down some steps and a few weeks later he complained of pain in his left hip which made walking impossible. He was admitted to a hospital where a tuberculous sacro-iliac joint and active pulmonary tuberculosis was diagnosed. He is a thin but well looking European. Temperature is between 97 and 99.8°F.; pulse 80 to 96. Sputum contains tubercle bacilli. The physical signs are dulness, bronchial breath sounds and crepitations over the right upper lobe.



FIG. 14. Upper left; FIG. 15. Upper right; FIG. 16. Lower left; FIG. 17. Lower right

An X-ray film showed extensive old-standing disease of the right upper lobe. The trachea was deviated to the right and there was a cavity one-half inch in diameter in the right infra-clavicular region. There were scattered small calcifications throughout the rest of the right lung. There was some scattered infiltration in the left apex and infra-clavicular region and scattered points of calcification throughout the rest of the left lung.

A bronchogram (figure 16) shows very thick pleura over the right upper lobe, bronchiectatic cavitation of this whole lobe and normal alveolar filling of the rest of the bronchial tree which is distorted by the upward pull of the atelectatic upper lobe.

A two-stage thoracoplasty was performed and figure 17 shows the condition after the complete operation; it will be noticed that the bronchiectasis did not disappear. Yet after the final stage the patient's sputum became negative and has remained so. He had instillation of sulphonamide suspension in lipiodol with each bronchogram, except the first.

Case 9: E.621, European female, aged thirty-four years. The onset of her illness was fourteen years before admission with temperature and dry cough. She was treated in various hospitals and sanatoria for about a year and had a right artificial pneumothorax for fifteen months. Five years later she began to cough again and two years later she had an hemoptysis. She is an ill-looking, cyanosed, dyspneic European woman. Her temperature and pulse are normal. The sputum contains tubercle bacilli. The physical signs are dulness and bronchial breathing over the right upper lobe and numerous crepitations in this area. The apex beat is shifted to the right.

An X-ray film showed chronic fibroid phthisis of the right upper lobe with deviation of the trachea, mediastinum and heart to right.

A bronchogram showed an atelectatic upper lobe, the seat of extensive bronchiectasis, an atelectatic lower lobe, also bronchiectatic, and a few bronchi representing the middle lobe. There was such destruction and distortion of the bronchial tree that it was difficult to make out landmarks.

A two-stage thoracoplasty was performed. The final result was that the bronchiectatic area in the upper lobe was largely collapsed but the lower lobe bronchiectasis remained untouched. At the end of the series of operations the patient's sputum was still positive. Instillation of sulphonamide suspension in lipiodol had been done between each stage and this was done twice more at intervals of a fortnight after the final operation. Her sputum then became negative.

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Part 2 will appear in the next issue

ANATOMICAL STUDIES ON HUMAN TUBERCULOSIS¹

XVIII. Additional Observations on Progressive Primary Pulmonary Tuberculosis in Adults

KORNEL TERPLAN

In two preceding papers (1, 2) the anatomical picture of true reinfection tuberculosis was presented. It was shown that in the pathogenesis of these various lesions, brought about by intracanalicular spread or by hematogenous seeding, or by a combination of both, exogenous pulmonary reinfection played the leading rôle, while the primary complex, with all its components in a completely obsolete state, had obviously no genetic relation to the active tuberculous lesions which were the major postmortem findings.

In a previous paper (3) on recent progressive primary tuberculosis in adults, a few brief anatomical reports were included, together with a chart of primary complexes found incidentally in 16 cases, which pointed to "late" primary infection apparently well beyond the age of childhood or adolescence. The conclusion drawn on the basis of these findings was that the course of primary infection in adults is not necessarily influenced by the age factor. Progressive primary complexes with overwhelming miliary tuberculosis and tuberculous meningitis or with direct intrabronchial extension, just as it occurs in primary tuberculous infection of children, and relatively recent fibrocased or cheesy-chalky complexes were seen in adults, and the involvement of the bronchomediastinal lymph nodes regional to the primary focus did not appreciably differ in extent or degree from that observed in children. The literature on primary tuberculosis in adults was cited, stressing in particular the work of Ghon and his pupils, Roman and Pototschnig, of Puhl, the views of Kuess, Ranke and Hart, and the papers of Ragnotti and of Frimann-Dahl. In the last four years there appeared only a few additional reports on acute progressive primary tuberculosis in young adults. Bernoulli (4) found in 3 young soldiers in a military training camp the typical picture of rapidly progressive primary tuberculosis with a recent primary complex, terminating in tuberculous meningitis. Koester (5) described the development of malignant primary tuberculosis in 12 patients between fourteen and nineteen years of age from a rural district. All were from families free of tuberculosis. When they left school, their tuberculin tests had been negative. The "childhood type" of tuberculosis was found postmortem in 27 cases among 113 adult Jamaican Negroes by Wells (6). There was a considerable incidence of primary cavitation. In 2 out of 3 cases of miliary tuberculosis of the childhood type, the site of the primary focus was not found.

That generalization of primary tuberculous infection follows in the majority relatively closely, though—with exceptions in childhood—not immediately, the

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TABLE 1
Anatomical findings in 7 cases of progressive primary tuberculosis in adults

CASE NUMBER	AGE, RACE, SEX	PRIMARY COMPLEX	EXTENSION IN THE LUNGS	HEMATOGENOUS SPREAD	SPECIAL REMARKS
2468	20 colored F	Pea-sized caseated focus, right lower with central cavitation. Massive caseation of all regional bronchopulmonary, lower and upper tracheobronchial lymph nodes	No intrabronchial extension	Overwhelming miliary tuberculosis in lungs, liver, spleen, kidneys, lower ileum and leptomeninges	Cause of death: tuberculous meningitis
2017	23 White F	Pea-sized, fibrocaseated subpleural focus, bases left lower. Diffuse caseated pleuritis around entire left lung. Only microscopic focal fibrous caseation in regional bronchopulmonary lymph nodes	Only restricted perifocal spread around the primary focus, especially toward the pleura. No intrabronchial extension	Massive miliary tuberculosis in lungs, liver, spleen, kidneys, left adrenal and leptomeninges	Death from tuberculous meningitis
3378	22 White M	Recent primary walnut-sized cavity, right middle. Incomplete caseation with large caseated conglomerate tubercles in the regional lower tracheobronchial lymph nodes	Extensive intrabronchial spread with tuberculous lobular pneumonia to all the lobes of the right lung and, in scattered fashion, to the lobes of the left lung	None	Complicated by congenital pulmonary stenosis
4484	23 White M	Recent primary cavity walnut-sized in right middle lobe. Extensive caseation of regional lower and upper tracheobronchial lymph nodes with perforation into the major bronchus	Localized intrabronchial spread to areas around cavity in middle lobe and to upper part of lower and apical portion of upper lobe. Left lung free	Only rare minute epithelioid cell tubercles in the liver	Extensive recent tuberculous ulcers in lower jejunum and ileum with perforation and extensive caseation of all mesenteric lymph nodes. Death from peritonitis following perforation

2530	30 Colored F	Cherry-sized, caseated focus with central cavitation in left upper, and massive intrabronchial spread through both subapical fields. Marked caseation of both upper tracheobronchial, paratracheal, anterior mediastinal and angulus lymph nodes	Typical tuberculous bronchitis and peribronchitis, entire left upper, apex left lower and upper half of right upper. Few recent acinous tubercles right middle and apex right lower	Isolated small cortical tubercles, left kidney	Massive caseation with slight chalky changes in all cervical lymph nodes. Larynx and trachea free. Softening of spinal cord at level of fifth and sixth thoracic vertebrae
2714	20 Colored M	Primary foci obscured. Cheesy-chalky tuberculosis in both bronchopulmonary, lower and upper tracheobronchial groups. Two chalky subpleural lymph nodules, one in right subapical area, the other in upper part of left lower	Several lentil-sized peribronchial tubercles in both upper lobes, the largest in the right subapical area close to the chalky lymph nodule, partly in chalky state	Dense miliary tuberculosis in both lungs, liver, spleen, kidneys and leptomeninges	Single recent ulcer in cecum. One of the primary lesions is obviously in the right apical area
5047	22 White F	About five caseated foci, 3 to 4 mm., in left upper (subapical field) with considerable caseation of regional lymph node groups including angulus lymph nodes	Intrabronchial extension to subapical field of right upper. Somewhat less marked caseation of regional right-sided lymph node groups	Dense miliary spread in both lungs, spleen, peritoneum, liver, leptomeninges, white matter of the brain. Hemorrhagic pleuritis	Recent progression to periportal and periaortic lymph nodes
5076	91 White F	No complex found. No chalky or calcified changes. One pea-sized cavity, right apex	Progressive apical and subapical, most marked in right upper lobe, extending into both lower lobes, especially left. Recent caseation of upper and lower tracheobronchial lymph nodes, both sides	None. Intestinal tract negative	Probably reinfection. Traces of old primary infection possibly obliterated

time of first infection was stated by Schuermann (7). In four-fifths of all cases of fatal generalized tuberculosis, Schuermann found the primary complex in a noncalcified state; in the remaining cases it was calcified.

The material used for this report consists of 8 cases. (Again, a few grossly most valuable observations could not be used for lack of sufficiently complete histological control of all pulmonary lesions concerned; therefore we did not feel justified in deciding whether the hematogenous pulmonary lesions found in these cases were secondary to the primary complex or whether they had originated from early superinfections.) Table 1 represents the postmortem findings in 8 instances, in 7 of which the primary lesion and the regional lymph node changes were in a recent caseated state. Of 3 of these (nos. 2468, 2017 and 3378) the anatomical findings were briefly given in our previous paper on recent primary tuberculosis in adults; another case (no. 5047) has already been discussed in detail in one of the preceding papers (on "focal extension"). In 3 out of the 8 cases listed in the table, the primary lesion had disintegrated into a cavity located in the upper portion of the left upper lobe in one, and in the right middle lobe in the 2 others. In these 3 cases there was considerable intrabronchial progression, one of them (no. 2536) showing great involvement of both sub-apical areas. Lymphogenous spread through the upper tracheobronchial and mediastinal lymph nodes, however, was in this case just as marked on the right side as on the left, which was the site of the primary cavity. Whether or not there was an additional complex of first infection, with primary lesions in the nasopharynx, pharyngeal tonsil, or in the upper pharyngeal wall, could not be determined due to restrictions at postmortem examination. All cervical lymph nodes showed extensive caseation with but slight chalky changes in a few of them. (Clinically there was no lesion seen, neither in the pharynx nor in the upper respiratory passages. The tuberculous nature of the lymph node swellings in the neck was diagnosed from a biopsy one year previous to death. Three weeks before the patient died, a block of the spinal canal at the level of the fourth dorsal vertebral body could be demonstrated roentgenologically, with typical symptoms of "transverse myelitis" due to compression. The tuberculous etiology of this myelitis was not ascertained, due to restrictions for adequate examination of the spine and spinal cord postmortem.)

In the 2 other cases with the primary cavity in the right middle lobe, lymphogenous progression was restricted to the side of the primary lesion.

Plate 1 represents two different levels in a horizontal plane cut through the primary cavity in one of these cases, a twenty-three year old white male (no. 4484). The gross and microscopic findings in this case will be briefly summarized.

There was a firmly caseated lesion in the lower-medial portion of the right middle lobe, of somewhat irregular outline, measuring in the fixed specimen $3 \times 2.2 \times 1.5$ cm. The centre of this lesion contained a cavity, the largest diameters of which were 2.5×1.5 cm.; it connected with the bronchus draining the right middle lobe. The border of the large caseated tubercle with the central cavity was indistinct and blended with focal hemorrhagic zones. Some areas of the adjacent lung parenchyma showed clusters of pinhead sized caseated tubercles contiguous to the capsule. The surrounding bronchi throughout

the right middle lobe were for the most part dilated, their walls considerably thickened; others contained various amounts of caseated material. The entire parenchyma of the



PLATE 1

right middle lobe had a rather firm consistency. The interlobar tissue appeared somewhat fibrosed and contained scattered tubercles in clearly peribronchial arrangement.

In the upper part of the right lower lobe near the junction with the middle lobe there were a few pinhead sized recent tubercles. The interlobar fissure between these two lobes was completely obliterated. In the right upper lobe there were a few clusters of grayish tubercles in the apical area, measuring from 1 to 3 mm. in diameter, with early caseation. The left lung was entirely free.

In the right major bronchus just below the carina, there were several circular ulcerations with a necrotic base and ragged, hemorrhagic edges. In addition, there were three shallow ulcerations from 5 to 8 mm. in diameter, anteriorly and to the right in the lower wall of the trachea, slightly above the bifurcation. There were also a few superficial ulcers in the wall of the right major bronchus, just opposite to the orifice of the bronchus draining the right middle lobe.

The lymph nodes at the hilum of the right middle lobe showed distinct caseation; they were moderately enlarged (2.0 x 0.5 cm.); in some of them there was considerable hemorrhage. Lower and upper tracheobronchial lymph nodes were also moderately enlarged and fairly completely caseated. The lymph nodes draining the left lung were free of tuberculosis.

The small intestine presented a typical picture of recent tuberculosis of the ileum and lower jejunum, with numerous circular ulcers from 1 to 5 cm. in width, with extensive necrosis of their bases extending into the subserous layer and with scattered typical hemp-corn sized tubercles in the serosa. There was a perforation of a tuberculous ulcer in the lower ileum, which appeared entirely covered by localized fibrinous adhesions with the omentum. There was recent fibrinous peritonitis with distention of the entire small intestine. All mesenteric lymph nodes showed extensive caseation, especially those immediately regional to the lowest ileum, which were about the size of a date.

The remainder of the anatomical findings included unusually severe lesions of gout involving all joints and the kidneys, and considerable marasmus.

Photograph "A" on plate 1 shows part of the primary cavity which had formed in the lumen of a second order bronchus. The entire wall of the bronchus is completely caseated, all its strata entirely necrotic, blending with the caseated content as well as with the interstitial tissue around the cavity. A large calibre branch of the pulmonary artery is in part included in this wall. At a somewhat lower level (B) the cavernous disintegration is much more marked. The extension of the cavity into the peripheral portion of the bronchus is seen in the centre of the photograph. The wall of the bronchus is still completely caseated here. A few lobules toward the lateral border of the middle lobe show distinct intrabronchial and peribronchitic caseated tuberculous pneumonia; others show various degrees of atelectasis. The considerable fibrosis of the interstitial tissue surrounding the primary cavity is noticeable in both pictures, also the ectasia with mucoid secretion in several smaller calibre bronchi. In these there are no specific lesions. Sections through the basal portions of the right middle lobe show the typical picture of fairly recent caseated peribronchitic tuberculous pneumonia, frequently with confluent tubercles, and again a few distinctly ectatic smaller bronchi filled with dense mucoid secretion. Sections taken through the trachea and the right major bronchus reveal typical tuberculous ulcerations in the membranous portion of both. One of the ulcers in the right major bronchus appears contiguous to the adjacent bronchopulmonary lymph node which is for the most part caseated. The bronchopulmonary and tracheobronchial lymph nodes show fairly complete caseation. The grossly noticed ulcerations in the trachea and central portion of the right major bronchus were apparently caused by direct extension of the large primary cavernous bronchial tubercle in the right middle lobe. A few small paratracheal lymph nodes to the right of the tracheal ulcers showed only acute congestion but no tuber-

culous changes. Only a few ulcerations in the right major bronchus appeared closely contiguous to a completely caseated bronchopulmonary lymph node. We have, therefore, in addition to direct extension from the primary cavity, a second source for bronchial tuberculosis from contiguous infiltration through the wall from the adjacent caseated lymph node.

In some parts of the primary cavity there were recent capillary hemorrhages in very close relation to the massive caseation, and a moderate amount of blood was intermingled with the necrotic debris in the cavity.

The histological picture of the tuberculous ulcers in the intestine showed extensive caseated tuberculosis with very marked destruction of both muscle layers and considerable thickening of the serosa. A few rare epithelioid cell tubercles were found in the liver only. The spleen showed severe changes of amyloidosis, mostly localized within the Malpighian follicles, apparently caused by the chronic gout, the microscopic changes of which were typical, especially in the pyramids of the kidneys.

The X-ray picture taken from the undissected specimen revealed only a considerable density around the right hilar area, lateral to and below the bronchus draining the right lower lobe. There are, nowhere, shadows pointing to chalky changes or calcification.

The entire gross and histological analysis proves the recent tuberculous infection in this case. The massive tuberculous ulceration in the small intestine is most probably secondary to the primary cavity in the right middle lobe. The symptoms pointing to the tuberculous infection, however, were first of an entirely abdominal nature, consisting of crampy pains starting three months previous to death. In the last weeks there were uncontrollable emesis and increasing anemia. Physical examination revealed impaired percussion above the right lower lobe with distinctly diminished breath sounds and coarse râles above both lower lobes. The patient had suffered for twelve years from progressive gout and was throughout this time under medical observation. No tuberculin test was made and no X-ray picture of the lung taken. It was not expected that the immediate cause of death was a tuberculous infection. A guinea pig inoculation with tuberculous material from the right middle lobe yielded a rapidly progressing tuberculosis, terminating in death of the animal on the twenty-ninth day following inoculation. Cultures were not taken.

In one of our cases (no. 2714), that of a twenty-six year old colored male who died from miliary tuberculosis and tuberculous meningitis, the anatomical findings pointed to two primary lesions. We were able to identify only one of them. There were two lentil-sized chalky nodules, one in subpleural position in the midportion of the left lower lobe, the other in the upper third of the right upper lobe about 2 cm. below the apex. These naturally were looked upon as presenting the primary pulmonary lesions. Histologically, however, they proved to be chalky-caseated intrapulmonary lymph nodules. There were considerable caseated and slight chalky changes in the bronchopulmonary and lower and upper tracheobronchial lymph nodes on both sides. The X-ray photograph taken postmortem showed fairly clearly the chalky subpleural lymph nodules in right upper and left lower lobe, while the chalky deposits in bronchopulmonary and tracheobronchial lymph nodes were only faintly noticeable. Histological analysis revealed one of the primary tubercles in very close relation to the chalky intrapulmonary lymph nodule in the right upper lobe. It was about of small pea size and was surrounded by a few small bronchial tubercles in typical peribronchial arrangement. There were very faint chalky changes in the centre of the lesion. Some of the tubercles in the left upper lobe showed also a rather typical peribronchial arrangement, with early disintegration in their centres. Both lungs were, in addition, densely seeded with miliary and small conglomerate tu-

bercles. Many miliary tubercles were also found in the liver, spleen and in both kidneys. There was typical tuberculous meningitis with ependymal tubercles in both lateral ventricles, but without involvement of the brain substance.

One of the primary lesions was unquestionably in the right upper lobe, while the primary focus tributary to the typical complex changes in the lymph nodes of the left lung was not found. The histological structure of both subpleural intrapulmonary lymph nodules, which showed more chalky substance than the other lesions, was that of typical, firmly caseated tuberculosis with rare epithelioid giant cell tubercles in the capsule of the lymph node. There was one small recent tuberculous ulcer in the cecum; mesenteric lymph nodes were free of tuberculosis.

The clinical history pointed also to a primary pulmonary infection, the first symptoms of which were noticed six months previous to death. There were persisting cough, night-sweats and distinct loss of weight. When the patient was admitted to the hospital a few days before he died, there was already distinct rigidity of the neck, and the X-ray film showed slight mottling over both lung fields, diagnosed as miliary tuberculosis.

We have added a somewhat unusual finding to this group of progressive primary tuberculosis—the last case in our table (no. 5076), that of a ninety-one year old white female. Postmortem, progressive apical and subapical tuberculosis was found, most marked in the right upper lobe, with a pea-sized cavity near the right apex and recent peribronchial tubercles in both lower lobes. Upper and lower tracheobronchial lymph nodes on both sides showed recent caseation. The peribronchitic tubercles were from hazelnut to cherry sized. The anatomical picture was first interpreted as a typical reinfection tuberculosis, apparently spreading from the cavity in the right apex throughout both lungs. Roentgenological examination failed, to our surprise, to reveal any remnants of a primary complex; there were, at least, no chalky or calcified scars, neither in the lung tissue nor in the bronchomediastinal lymph nodes. Intestinal tract and mesentery were also negative. Considering the high age in this case, it is possible that obsolete calcified remnants of an old primary complex might have been entirely resorbed.

Histological examinations of the cavity and the surrounding tuberculous lesions in the right upper lobe revealed older collapse-induration, along with fibrocased tubercles, and also a rare minute sequestered calcified bronchial cartilage included in the fibrous scars. The lymphogenous progression in the bronchomediastinal lymph nodes of both sides was as active as in any primary tuberculosis or in progressive reinfection.

An epicritical summary of our 7 cases of primary progressive tuberculosis includes the following anatomical types: Typical primary complex with only lymphogenous extension and with overwhelming miliary tuberculosis in 3, in one of these combined with recent localized intrabronchial focal extension; primary cavitation with typical complex changes and considerable intrabronchial spread in 3, in one of these complicated by deglutition tuberculosis of the small intestine with perforation of tuberculous ulcers and recent peritonitis; and a most unusual massive, caseated tuberculous pleuritis in connection with a primary fibrocased subpleural focus, leading to massive miliary tuberculosis, in one. The cause of death was tuberculous meningitis in 4, ulcerative tuberculous enteritis with perforation and recent peritonitis in one, and progressive intrabronchial pulmonary tuberculosis in 2. One of these latter was complicated by congenital pulmonary stenosis with typical cor pulmonale.

SUMMARY

The anatomical findings in 7 cases of progressive primary tuberculosis in the young adult from twenty to thirty years are presented. They resemble closely the anatomical character of progressive primary tuberculosis in children, including considerable lymphogenous spread from the primary lesion to the regional bronchomediastinal lymph nodes, cavitation of the primary focus followed by intrabronchial extension and overwhelming hematogenous miliary seeding with tuberculous meningitis. One unusual observation of caseated pleuritis contiguous to a recent primary parenchymal subpleural lesion—with but slight lymph node complex changes but with overwhelming miliary tuberculosis—is also included, and an apparently primary progressive phthisic form of pulmonary tuberculosis in a senile person, aged ninety-one, is added, suggesting that remnants of a primary complex may leave no grossly recognizable traces in later life, especially in senility.

SUMARIO

Preséntanse en este trabajo los hallazgos anatómicos en 7 casos de tuberculosis primaria evolutiva en jóvenes de 20 a 30 años de edad. Las características anatómicas son muy semejantes a las de la tuberculosis primaria evolutiva en el niño comprendiendo considerable propagación linfógena de las lesiones primarias a los ganglios linfáticos broncomediastínicos regionales, cavitación del foco primario seguida de difusión intrabronquial y extensión miliar hematógena agobiadora con meningitis tuberculosa. También se presenta una observación extraña de pleuritis caseada contigua a una lesión subpleural parenquimatosa primaria reciente—con leves alteraciones complejas de los ganglios linfáticos pero con granulia agobiadora—y una forma tísica evolutiva aparentemente primaria de tuberculosis pulmonar en un anciano de 91 años, que indica que los residuos de un complejo primario tal vez no dejen indicios macroscópicamente identificables en la vida avanzada y sobre todo en la senectud.

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BOOKS

HERMAN E. HILLEBOE AND RUSSELL H. MORGAN: *Mass Radiography of the Chest*. Pp. 288, with 93 figures, The Year Book Publishers, Inc., Chicago, 1945, cloth, \$3.50.

By PAUL C. HODGES

This little pocket-sized red book, with the fetching sketch on its cover, is a timely, authentic, highly usable text of which authors and publishers may well be proud. Chapters 2, 3, 10, 11 and 12 deal briefly with the whole problem of tuberculosis control and the administrative aspects of chest surveys; the rest of the book is devoted to a history of mass radiography, the details of its present-day application and a guess as to what its future development may be. The index of eight pages is well planned and as complete as it is reasonable to hope for in these days of paper and labor shortage.

The reviewer is intimately acquainted with the authors and their work and, therefore, is a prejudiced critic, but no reader can fail to appreciate the excellence and freshness of such portions as Chapter 6, which is entitled *Physical Factors Affecting the Choice of Equipment* but is, in fact, a concise, though thorough explanation of the physical factors concerned in the formation of X-ray images.

Radiologists, chest specialists, superintendents of hospitals and sanatoria, lay members of agencies connected with tuberculosis control, X-ray technicians and servicemen—all these can and will read the book with profit to themselves and incidentally to the authors and publishers, who will probably have to reprint again and again.

R. R. TRAIL, H. J. TRENCHARD AND J. A. KENNEDY: *Mass Miniature Radiography. A Practical Handbook*. With Foreword by Lord Dawson of Penn. Pp. viii + 96, with 24 illustrations, London, J. & A. Churchill Ltd., 104 Gloucester Place, Portman Square, 1943, cloth, 8s. 6d.

By IRA LEWIS

It is a far cry in mass miniature radiography from the determination of exposure factors by dead reckoning to the automatic selection of optimum factors by means of the phototimer. To this extent has this small handbook become outdated.

This volume describes the organization and operation of a mass miniature radiography unit. Much time is spent on the follow-up of positive cases. It is questionable whether this problem in its ultimate detail is a part of the function of the mass radiography unit. It is also felt that the determination of an individual's fitness for work is outside the realm of the unit. Certainly these subjects do not deserve lengthy discussion in a volume of this size.

The chapter on interpretation of miniature films is recommended for all who are neophytes at this type of work. There is quite a variation in viewing a

miniature film in comparison with a conventional roentgenogram of the chest. The authors describe many of the pitfalls encountered in miniature film viewing that are not considered in any known work at the present time.

Although much of the text needs revision in view of our present standards of equipment, the remarks of Lord Dawson of Penn in discussing mass radiography units, in the Foreword to the text, are noteworthy.

"It is none the less to be hoped that the departments will be linked to, if not located in, appropriate hospitals in an area large enough to command a complete pattern of health and hospital services, and including, where possible, the intellectual leadership of a teaching (University) hospital. They would thus afford an example of that closer co-ordination of hospital and public health services—of curative and preventive medicine—essential alike to the progress of medicine and the welfare of the community."

EDOUARD RIST: *Les Symptomes de la Tuberculose Pulmonaire. Clinique, Physiologie Pathologique, Thérapeutique.* Pp. xvi + 594, Masson & Cie, Paris, 1943.

By MAX PINNER

The medical voice of France could not be heard in this country for more than four long years. Now that communications are being reestablished, one of the first books in our field is by Doctor Edouard Rist, an unchallenged leader in tuberculosis work. It is a good omen that this book, with which broken contacts are initiated again, is one of great stature, of mellow maturity and clinical wisdom.

It may come as a surprise that a book of nearly 600 pages should bear the title *The Symptoms of Pulmonary Tuberculosis*, but the subtitle *Clinic, Pathological Physiology and Therapy* more clearly indicates the real scope of this work. In the introduction, Doctor Rist says: "Taking the symptoms as theme, I have endeavored first to describe them in their nuances and their variations, to place them properly within the development of the disease, to define the orientation they give in practice in the study of clinical signs and the establishment of diagnosis, to show how observing them guides prognostication and controls the effects of therapy. In one word, I have made a clinical study of them." He goes on to say that "each symptom is correlated with its causes, analyzed in its origin and mechanism, interpreted in terms of its underlying dysfunction."

The symptoms of pulmonary tuberculosis are, in fact, simply used as raw material for thorough discussions which are mainly in the nature of pathological physiology. These discussions are exhaustive, fundamental and always lucid. They frequently penetrate to basic questions of normal physiology, anatomy, pharmacology or whatever discipline may help to clarify any given subject and, at times, they are the starting points for interesting digressions into biography and literature.

The important symptoms of pulmonary tuberculosis are presented in great

detail; they are evaluated, explained and analyzed in such a thorough manner that the total result is an almost complete text-book on pulmonary tuberculosis. The symptom of cough, for example, is discussed on 25 pages, that of hemoptysis on 53 pages and that of dyspnea on 159 pages. The entire subject matter is centered around symptoms; hence the orientation is unique and, I believe, extremely pertinent. It is altogether the mightiest counterweight against modern tendencies that might eventually turn the clinician into a desk-worker with direct wires to laboratories and roentgenological departments.

Doctor Rist has not only fully accomplished the task that he outlined for himself, he has written a book of profound interest and of a particular charm. Its charm is not easily analyzed. It is not only due to its graceful style, its clarity of expression and its careful planning and disposition of each subject matter. There are, in addition, a mental simplicity and an intellectual directness, well balanced discrimination between the fundamental and the accidental details; an alert sense for the historical development and a profound respect for the work of important authors. "But I can say, at least this: I have read the authors whom I quote. I have endeavored to translate exactly their thoughts. As much as possible I have made them speak themselves, even at the risk of appearing long-winded; and in the discussions I have presented the discussors. Science is built by human beings. One does not do justice to them if one reduces history to a dry catalog of facts and names." And, in a footnote, Doctor Rist adds: "I have always been troubled by the habit that so many medical writers have to extricate themselves from all serious and living bibliography by simply putting an enumeration of names in parentheses following the expression of an opinion, a doctrine or a scientifically derived fact. This procedure is not even polite in regard to the readers. It is discourteous towards the authors."

Doctor Rist has not attempted to accumulate an all inclusive bibliography; he presents a strictly selective list and, in accordance with the principles just quoted, he frequently adds some fascinating biographical sketches. Doctor Rist's book is so lively in tone not only because he is master of a lively style but because he recreates so well the lives of pertinent authors.

E. M. BRIEGER: *The Papworth Families. A 25 Year Survey. With a Preface by Sir Arthur Salusbury MacNalty.* Pp. xii + 674, London, William Heinemann—Medical Books, Ltd., 1944, cloth, 45 sh. American Publishers: Grune & Stratton, 381 Fourth Ave., New York, New York, \$11.00.

By MAX PINNER

The nucleus of Doctor Brieger's book consists of a detailed clinical report of all the members of all the families that have lived in the Papworth Village Settlement during the twenty-five years between 1913 and 1938. Particular emphasis is given to the fate of the children who lived or were born in the Village, since the

feasibility of such tuberculosis settlements depends largely on the demonstration that such children are not doomed to high morbidity and mortality from tuberculosis. In the Papworth study extensive use was made of periodic health examination, including roentgenological studies and tuberculin tests.

The entire child population consists of 368 children of whom 108 were born in Papworth, while the remaining 260 were born before admission to the Village. Of the total, 32 were children of the healthy staff, 77 were exposed in their families only to sputum-negative or surgical patients and 151 children had one or more sputum-positive patients in their families, while, as stated before, 108 were born in the Village. It is most impressive to find that, in the whole group, only 5 children had active "childhood tuberculosis" (one in the group exposed before admission to sputum-negative cases and 4 exposed to sputum-positive cases) and 9 developed "adult phthisis;" the latter were all exposed to sputum-positive cases before admission. Of the 108 children born in the Village, 2 had "transient perifocal reactions," 5 showed "residua of primary infection," but none developed frankly active processes; the incidence of radiologically demonstrable calcified foci was 42.6 per cent.

These are some of the basic data which seem to be of prime interest. Doctor Brieger presents, of course, a most detailed analysis of these data according to age groups, duration of residence, etc. He also explains the socio-economic background of the settlement.

This factual report forms part 2 of the book and occupies 82 pages. In addition, Doctor Brieger presents in the Appendix the records of 244 families, most of them in the form of epidemiological family charts of the kind which Doctor Opie and his associates first used in their epidemiological studies in the Phipps Institute in Philadelphia.

This meticulously careful presentation of the raw data will make it possible for statisticians to decide to what extent general conclusions may be based on this material. On its face value it seems obvious that the Papworth experiment has demonstrated that, given proper conditions, children can live in a tuberculous milieu without incurring an excessive tuberculosis morbidity. However, Doctor Brieger justly points out that the majority of children have not reached maturity and that further observations will have to determine their eventual fate in the critical ages of puberty and adolescence.

To quote from the Preface by Sir Arthur Salusbury MacNalty—"Dr. Brieger has not been content to present this remarkable survey by itself. He has penned a copious historical introduction, and discussed at length epidemiological considerations and pathological implications, some of which have led him far afield from the main subject of inquiry while others are of a highly controversial nature."

One may add that the historical introduction of some fifty pages does not deal with tuberculosis settlements or rehabilitation schemes but ranges far and wide through the history of the pathology and clinic of tuberculosis, tracing the opinions concerning the contagiousness of tuberculosis, starting unavoidably

with Hippocrates. This introduction does not clarify the subject; it contains statements of most questionable validity, for example on p. 18, "there can be no doubt that he [Hippocrates] was describing the caseous focus in the lung which we call today 'round focus' or tuberculoma" [that is, when he speaks of phyma]; this discussion has tenuous, if any relation to Doctor Brieger's Papworth study. The "epidemiological considerations and pathological implications" are not only "highly controversial" but, to a large extent, not pertinent; they lack, in this reviewer's opinion, lucidity and perspective; they do not add to, but rather detract from the solid validity of the Papworth study itself. They are the kind of discussions in which one may well indulge *in camera*, but they are hardly sufficiently ripened nor documented for published conclusions. As examples one may mention the vague and rather confusing paragraphs on *The Nature of Round Foci* or the ill defined usage of the terms "initial focus" and "initial phase" which are apparently used at times in reference to the primary lesion (or infection) and then again in reference to incipient clinical disease.

It is necessary to return once more to the solid factual observations of the Papworth children—not only to stress again their value, but also to lodge a protest against some features of poor technical organization of the presentation. It makes reading and understanding unnecessarily difficult that the numerous tables are treated in five different ways: (1) tables in the text, numbered as is customary; (2) *idem*, but, for unexplained reasons, not numbered; (3) tables numbered and with an asterisk which, one learns by referring to a footnote on p. 74, are contained in the Appendix and, since no page numbers are cited, are difficult to find in a book of some six hundred pages; (4) tables in the bibliography, numbered according to the original publications in which they appeared; (5) *idem*, but not numbered. One may add a sixth type of table, namely, absent ones. Table 7 which is repeatedly referred to in the text, and contains apparently important information, could not be found anywhere in spite of careful search by three persons.

The bibliography also is not arranged for the reader's convenience: part of it is annotated which is most welcome; but if one wishes to know author, title and place and time of publication one is obliged to look in two or three different places.

The factual information which this book contains is worthy of widest publicity. The Papworth work is fundamentally important and might well serve as shining example for future, much needed rehabilitation projects. The clinical experience of the first twenty-five years of its existence is knowledge that should be available to all workers connected with rehabilitation and its epidemiological implications will have to be considered in future discussions.

A simple report of the facts, stripped of all speculative introductions and conclusions, would probably more easily reach all those who should read it.

ALVAN L. BARACH: *Principles and Practices of Inhalational Therapy*. Pp. xvi + 315, with 59 illustrations, J. B. Lippincott Company, Philadelphia—London—Montreal, 1944, fabrikoid, \$4.00.

By GEORGE C. LEINER

Inhalational therapy is being used in modern medical practice to an ever increasing extent. Doctor Barach states in the preface that "this book is intended for physicians who wish to understand the physiologic basis as well as the technics of inhalational therapy." This purpose has certainly been achieved by the author who by his investigations has contributed much to the rapid progress in this field. After a chapter on *Historical and Physiologic Background of Inhalational Therapy*, the pathological physiology and the advisable method of inhalational therapy are presented for conditions such as altitude sickness, pneumonia, edema of the lungs, congestive heart failure, coronary thrombosis, shock, pulmonary infraction, massive collapse of the lung, postoperative atelectasis, bronchial asthma, obstructive lesions in the larynx, trachea and bronchi, pulmonary emphysema, accidental asphyxia, asphyxia of the newborn, hemorrhage, peripheral arteriosclerosis, migraine, seasickness, gas gangrene, tetanus, war-gas poisoning and many more. In the chapter on pulmonary tuberculosis, Doctor Barach's recent experience with the equalizing-pressure chamber is presented. In other chapters, the different methods, gases and apparatus used for inhalational therapy are described in detail, so that the book is of real interest and value not only to physicians but also to nurses and technicians who handle the equipment. There is a chapter on *Research in Respiratory Function and Inhalational Therapy*, which stimulates further experimental and clinical studies. Each chapter is followed by a bibliography and there is a good index. This book is timely and practical; it covers comprehensively inhalational therapy, as could be expected from an author who himself has such an extensive experience in this field. It is particularly commendable that both the fundamental and practical features are presented concisely and lucidly. This book should be kept handy next to each gas tank used for treatment.

HARRY S. MUSTARD: *An Introduction to Public Health*. Second Edition. Pp. ix + 283, New York, The Macmillan Company, 1944, cloth, \$3.25.

By IAGO GALDSTON

Harry S. Mustard's *Introduction to Public Health* is precisely what its title represents it to be, a work designed "to orient the student in the field of public health." It offers the reader a background of information and the premises for a philosophy of public health. Of the two, information predominates. The reverse would have been preferable, for the beginner is much more in need of understanding than of bulk knowledge. Besides, Professor Mustard is a sage and eloquent philosopher, and in following the text one comes upon many nuggets of fine writing and wise insight which are both delightful and stimulating. The

Introduction to Public Health can also be described as a small encyclopedia on public health. The 23 pages of the index show how large a field the book covers and, incidentally, the index itself adds greatly to the value of the work. As is to be expected, in some parts the work suffers because of its brevity. It isn't possible to do "justice" to the subject of health education in two pages of text, nor to the public health aspects of mental disease in like length.

On the other hand, the book is an Introduction. The handicap of brevity could be amended by an extensive bibliography.

In this respect the book falls short of its otherwise high merit. The work can be warmly recommended to the student in public health and more particularly to all those who are ancillary workers in the fields of "health and medicine," such as health educators, biology teachers, social workers and nurses.

STAFFORD L. OSBORNE AND HAROLD J. HOLMQUEST: *Technic of Electrotherapy. And Its Physical and Physiological Basis*. Pp. xix + 780, with 240 figures and 72 tables, Charles C Thomas, Springfield, Illinois—Baltimore, Maryland, 1944, cloth, \$7.50.

By KARL HARPUDER

The authors, teachers of Physical Medicine at the Northwestern University Medical School, although not physicians, have succeeded in this volume of approximately 750 pages to give the medical profession and the technicians a scientific, clear and sufficiently but not superflously detailed course in Electrotherapy.

The book consists of four parts dealing with Direct Current, Electric Muscle Stimulation, Radiation and High Frequency Currents, respectively. The physical principles of electrotherapy are carefully and comprehensively explained in the text, while the initiated or more arduous student will find further instruction in footnotes. The known physiological effects of each modality are critically discussed and, as a rule, this review on physiology reaches the high standards of the chapters on physics. Indications and contraindications of therapeutic applications are briefly enumerated and the techniques of application thoroughly explained.

Because the book offers so much and so valuable information to the serious student in electrotherapy, the reviewer likes to make some critical suggestions. Why does muscle stimulation occupy one of the four main parts of the book which is otherwise subdivided on physical principles? The detailed discussion of electrophysiology is not quite up to date and entirely neglects nervous conduction and transmission. Clinical observations of little value are quoted with some frequency, for example, pages 37, 62, 159, 160. A few errors appear in scattered places: for example, page 31, conduction in a solid conductor depends upon free ions; or page 33, perspiration, an excellent electrolyte. These are only minor criticisms. The book is highly recommended for the physician and the medical student who wants to familiarize himself with electrotherapy.

RUDOLF A. STERN: *Trauma in Internal Diseases. With Consideration of Experimental Pathology and Medicolegal Aspects.* Foreword by Francis Carter Wood. Pp. xxiv + 575, Grune & Stratton, New York, 1945, cloth, \$6.75.

By EMANUEL GOLDBERGER

This volume attempts to describe the relations between nonpenetrating trauma and the development of internal disease. Doctor Stern does this by means of an exhaustive survey of the American and European literature, his own wide experience and postmortem observations.

The book is divided into twenty chapters. There are separate chapters for diseases of the heart, arterial diseases, diseases of the veins and essential hypertension. Then follows a discussion of diseases of the lungs and pleura, diseases of the gastro-intestinal tract, liver, biliary system, pancreas, and chapters on appendicitis and peritonitis. The remainder of the book discusses kidney diseases, malignant neoplasms of internal organs, disorders of metabolism and, finally, diseases of the blood and lymphatic system. A big order!

There are many difficulties that beset the path of him who tries to establish relations between an injury or an accident and the development of a disease process in an internal organ. One of the biggest barriers that has hindered knowledge of these relations is the economic and very real issue of compensability which hangs like a heavy cloud over the entire field. It would be a wise man who could divorce compensability from the determination as to whether a cause-effect relationship existed between an injury and the development of disease in the internal organ. Even when postmortem observations prove the presence of disease it does not necessarily follow that trauma was either the sole cause, a contributing cause or an aggravating cause of it. This is true throughout the entire field of internal medicine.

While it is reasonable to assume that rupture of an otherwise normal heart in a boy of 10 who had been knocked down and stepped upon could be due to this injury (page 38), it is questionable whether a blow on the head which resulted in no abnormal neurological signs and no alterations of spinal fluid was the cause of hypertension of "traumatic" origin due to "an injury to the vasomotor centre (small hemorrhage?)" (page 181). The author feels that severe physical strain can lead to the same injuries of internal organs as external trauma which compresses the chest or abdomen. This may be true but it is a very difficult matter to prove.

After perusing the book one comes away with the feeling that in cases where the relations between trauma and internal disease are not completely established the author tends to favor the injured workman. Such an attitude is laudable, but good intentions do not always fall within the realm of scientific procedure. Throughout the book there are cited many of the decisions handed down by the courts and workmen's compensation boards concerning the relations between trauma and internal disease. Doctor Stern rightfully dissents from many of these decisions. Here again, the processes of legal reasoning do not necessarily run parallel to the methods of scientific observation.

The book is of interest to the legally-minded physician and to the lawyer who deals with medico-legal problems.

Brief Comment

Tuberculosis in the United States. Graphic Presentation. Volume 2. Proportionate Mortality Statistics for States and Geographic Divisions by Age, Sex and Race. Prepared by the staffs of the Division of Public Health Methods and the Tuberculosis Control Division, U. S. Public Health Service, under the direction of Carroll E. Palmer, M.D. Medical Research Committee, National Tuberculosis Association, 1944, paper.

The following paragraphs, reprinted verbatim from the Foreword, state clearly the purpose and scope of the present volume.

"The volumes in this series, *Tuberculosis in the United States, Graphic Presentation*, are the result of a cooperative undertaking by the National Tuberculosis Association and the United States Public Health Service. The basic data were made available by the United States Bureau of the Census.

"The first volume of the series presented, for each State, tuberculosis mortality rates by age for the several race and sex groups. Such rates relate tuberculosis deaths to their corresponding populations and are without doubt the best indices of the current status and of changes in tuberculosis mortality. However, the accurate data on population composition required to compute mortality rates specific for age, sex and race for given localities are available only for the census years, and rates for intercensal years become progressively less reliable. Furthermore, population shifts brought about by the war make population estimates even more unreliable so that it has become difficult to evaluate trends in tuberculosis mortality in many parts of the country. Consequently, there is need for a usable index of the trend and current change in tuberculosis mortality which is independent of population enumeration. The present volume is an attempt to meet that need by means of 'mortality ratios,' usually known as 'proportionate mortality,' which relate tuberculosis deaths to deaths from all causes."

"The present volume presents two charts and one table for the United States, each geographic division, and each State. The table contains, for each of the three-year periods, 1919-21, 1929-31 and 1939-41, the number of deaths from all causes and the percentage of those deaths that are due to tuberculosis (all forms) by age, sex and race. Comparable distributions of the number of deaths from tuberculosis (all forms) are available from Volume 1 in the series. The charts in this volume present for each area:

4. Deaths from tuberculosis (all forms) as percentages of deaths from all causes, by age, sex and race, 1939-41.
5. Deaths from tuberculosis (all forms) as percentages of deaths from all causes, by age, 1919-21, 1929-31 and 1939-41.

"For the period of 1939-41, three additional charts are included; these present

by State the proportionate mortality from tuberculosis (all forms) standardized for age. The first is a map chart, giving this standardized ratio for all races. The other two are bar diagrams, one for the white group in each State, and the other for the nonwhite group in each State with an enumerated nonwhite population of 100,000 or more in 1940. The distribution by age of the deaths from all causes, for both sexes and all races, for the period of 1939-41 was selected as the basis for the standardization. The small and insignificant proportion of deaths from tuberculosis among persons of unknown age was disregarded in calculating the standardized rate."

Books Received

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HAROLD M. CAVINS: National Health Agencies. A Survey with Especial Reference to Voluntary Associations. Including a Detailed Directory of Major Health Organizations. Pp. 251, Public Affairs Press, Washington, D. C., 1945, cloth, \$3.00.

KATHLEEN C. CLAR, P. D'ARCY HART, PETER KERLEY AND BRIAN C. THOMPSON: Mass Miniature Radiography of Civilians. For the Detection of Pulmonary Tuberculosis. (Guide to Administration and Technique with a Mobile Apparatus Using 35 mm. Film: and Results of a Survey). Pp. 135, with 51 figures and many tables, Medical Research Council, Special Report Series No. 251, London, His Majesty's Stationery Office, 1945, paper, 3s. 0d.

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Report of the Committee on Rehabilitation

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Rehabilitation is defined by the National Council on Rehabilitation as the "restoration of the handicapped to the fullest physical, mental, social, vocational and economic usefulness of which they are capable."

The Committee is of the opinion that rehabilitation of the patient rightly begins in the clinic after the diagnosis of tuberculosis has been made. It is further believed by the Committee that a strong social service department in the clinic is an important part of the rehabilitation program. Frequently the medical social worker assists the patient toward gaining an insight into his social, economic and emotional problems and helping him toward a solution of them. After this he is better able to make decisions regarding his future medical care and, perhaps, a new way of life.

Any good in-sanatorium rehabilitation program should include several closely related activities: social service, occupational therapy, vocational testing, counseling and prevocational training of various types, and patients' educational activities. The ultimate aim is to find patients' vocational possibilities and to see that necessary training is obtained, so that employment may become available when the patient's physical condition permits and after training has been completed. If these occupational plans are carried out the dangers of relapse are greatly diminished. The program has a distinct practical value to the community and to the nation, for it is definitely a part of the tuberculosis control program as well as a part of the program to insure manpower. In addition, it provides a goal for the patient which aids in maintaining his morale and in obtaining his coöperation in the prolonged treatment required in tuberculosis.

Even though we have known the unmet needs of our disabled tuberculous patients and have charted for many years workable plans for their rehabilitation, these needs have remained unmet. The chief reasons for this failure may be given as follows:

- 1: With the exception of the physical restoration of the patient the physician has shown a lack of interest in a planned program of rehabilitation.
- 2: This may in part have been due to the fact that governing boards and health departments could not find sufficient funds for their budgets for purposes other than case-finding and treatment of the physical condition.
- 3: This attitude also may have been due to the fact that, in many small and some large institutions where there is a lack of beds for the tuberculous, the turnover of patients is too rapid to make an in-sanatorium rehabilitation program workable.

Such causes for failure and the inequities in the general program of rehabilitation will undoubtedly continue. With the passage, however, of the Barden-

LaFollette Act of 1943 by Congress, we have for the first time a firm foundation on which a constructive program of rehabilitation may be built.

The Barden-LaFollette Act provides for the rehabilitation of disabled civilian tuberculous patients, as well as others, on a federal-state basis. This applies to any civilian patient, regardless of whether he is in a private or governmentally administered institution, or whether he is under the care of a private physician. The federal government is permitted to assume all necessary state administrative costs and the cost of vocational advisement and counseling. The cost of vocational training, however, is shared by the state and federal governments on a fifty-fifty basis. Vocational counseling, training and placement are available at no cost to the civilian tuberculous patient. This service is available not only to patients who have been discharged as apparently arrested or arrested cases in the state post-sanatorium program, but it is available to in-sanatorium patients who have a good chance for recovery and who may be accepted while still in the sanatorium by the state department of vocational rehabilitation as clients. The extent to which any state department of vocational rehabilitation may go in its training program, both in and out of the sanatorium, will be dependent upon the amount of money made available to it by the state legislature.

In addition to the above, we have been informed that the U. S. Public Health Service, through its new Bureau of Tuberculosis Control, will furnish grants-in-aid to tuberculosis out-patient clinics where such requests are made through the state health officer and when such requests are approved by him. Medical social workers and clerks may be obtained in this way.

It is the Committee's recommendation that medical directors of sanatoria who have not already done so make plans for organizing both in-sanatorium and post-sanatorium rehabilitation services for their patients. The Committee recommends that the larger institutions should have departments established within them with full-time personnel for the most part. For small sanatoria where this might not be practical, it will be possible, according to information received from one of the regional representatives of the Office of Vocational Rehabilitation, to obtain the services of key workers on a part-time basis through the state agency. Medical directors are urged to contact their state department of vocational rehabilitation for the purpose of securing the latest information relative to the establishing of rehabilitation programs according to their particular needs.

Notices of the availability of vocational rehabilitation services through the state department of vocational rehabilitation have been published by the Committee on Rehabilitation of the American Trudeau Society in the News Letter.

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Prophylaxis of Tuberculosis in School Children.—A review of the achievements in the field of school hygiene and medical supervision of teachers and school children during the past forty years is given. Much pioneer work, largely due to Doctor Martirene, has been done. Physical conditions of the pupils of many schools have been thoroughly investigated. Vacation colonies have been instituted. In 1927 systematic BCG vaccination of school children was started and has proved to be helpful. The investigation of a school takes five weeks. In the first week the children's parents are called to meetings and are given lectures about tuberculosis and the necessity for medical examination of the children, including tuberculin tests. After the parents' consent has been obtained, each pupil and teacher is skin-tested (Pirquet) and is given a complete physical examination. A special record about the anamnesis, the social and economic conditions of the family and their health status is filled out by social workers and kept on file. During the third week a modified Mantoux test (1:100 and 1:10) is given to all doubtful or negative cases and the results are read. During the fourth week all children are X-rayed with a portable X-ray machine at a rate of about 200 a day. In the fifth week, special X-ray pictures and further examinations are made for all those with dubious X-ray findings. Their families are examined, also. The private physician is advised and all children with negative skin tests and normal X-ray pictures are given BCG vaccine. This vaccination is given to the nonallergic patients of all ages, as it is considered the most effective measure against tuberculous infection. Tuberculin reaction occurred among 8,724 children between 6 and 14 years of age in 37.2 per cent. The rise of

the positive skin test is very steep from the twelfth to the twentieth year of life. It is 46.6 per cent in boys and 43.3 per cent in girls in their twelfth year. In the twentieth year it is 79 per cent in men and 82.9 per cent in women. In the age group from 14 to 16 it is 67.4 per cent and in the age group from 16 to 20 it is 80.4 per cent. It has been observed that among young women the frequency and the severity of the infection is markedly higher than in young men. Of 8,724 pupils examined during the years 1940 to 1942, 3,123 had a positive skin test. Of them, 588 (18.8 per cent) were tuberculous; 204 (6.5 per cent) had suspicious X-ray pictures; 169 or (5.34 per cent) were suspected of activity or active; 24 (0.76 per cent) were frankly progressive and 191 (6.1 per cent) had residual tuberculosis. As there are 60,000 pupils in the public schools of Uruguay it may be anticipated that about 3,000 of them are tuberculous and need immediate medical attention or sanatorium treatment. Of all those with proved tuberculous lesions, 29.2 per cent had a positive tuberculin test. It has been found that between 2 per cent and 3 per cent of teachers have active lesions and at least 1 per cent have sputum positive for tubercle bacilli. Amongst the student teachers, 6.7 per cent were suspects and of those, two-thirds had tuberculosis. Each teacher who is found to have a lesion is given a three-year vacation, but in view of the precarious economic condition of the majority of the teachers, they generally cannot benefit from a sanatorium cure and are forced to accept other work during this period. —*Profilaxis de la tuberculosis en el medio escolar, L. M. Petrillo, Bol. Inst. internac. am. de protec. a la infancia, September, 1944, 18: 445.*—(W. Swienty)

Photoröntgen Chest Examinations.—One hundred thousand consecutive routine photoröntgen examinations of the chest of men reporting to an Induction Station were reviewed by the authors. They believe that this method, using 4 x 5 inch stereoscopic films, has made the older method obsolete. Not only is there economy in the smaller film, but the concentrated field of vision, the sharpness and definition of the image, the rapidity and accuracy with which interpretation can be made, and the minimum of eye fatigue are added factors favoring this method of examination. A Lysholm grid was used in all examinations and added to the excellence of the film quality. The rejection rate for pulmonary tuberculosis in this series was 4.91 per thousand examined, including all types of disease from far advanced active cases to the chronic minimal fibrous or apparently arrested cases in which stability of the lesions was not yet demonstrated. Among the non-tuberculous conditions of the lung and pleurae, 3.55 per thousand were rejected. Abnormalities of the heart, pericardium and great vessels were found resulting in a rejection rate of 3.87 per thousand. The low rejection rate at this station reflects creditably on the antituberculosis program in North Carolina and also on the screen-out of known tuberculous selectees at the local boards. The economy and facility of accurately diagnosing pulmonary disease with this method without recourse to the more expensive 12 x 17 inch films is to be considered in view of the reported increase in tuberculosis since the onset of the war especially in Europe, and the predictions of others, including Plunkett who maintains that "tuberculosis will assume the proportions of a plague in Europe as the war progresses."—*A Statistical Analysis of 100,000 Examinations of the Chest by the Photoröntgen Method*, P. Zanca & F. K. Herpel, *Radiology*, August, 1944, 43: 122.—(G. F. Mitchell)

Survey of "Healthy" Persons.—In the dispensary of Palencia 2,004 persons, supposedly healthy, were examined. Of 704 contact cases, 97 (15.9 per cent) were found to be

tuberculous; 64 of these (19.2 per cent) were children. Of another group of 1,300 people who had no known contact with tuberculosis and who were taken from different parts of the population, 38 (2.9 per cent) were found to have active tuberculosis. The Mantoux test was given to a group of 1,255 supposedly healthy persons and more than 75 per cent were positive. It is interesting to note that throughout Spain mass examinations with intracutaneous tuberculin tests proved to be positive in 51 per cent to 73 per cent of those tested, according to the different authors.—*Nuestros resultados en la investigacion sistematica en personas supuestas sanas*, B. Urzay & D. Opacio, *Rev. de Sanidad e Higiene Publica*, March-April, 1944, 18: 147.—(W. Swienty)

Tuberculosis Survey among Healthy Persons.—In several South American republics systematic physical and X-ray examinations have been conducted in a large number of communities of supposedly healthy people. A surprisingly great amount of inactive and active pulmonary tuberculosis was detected which had never been diagnosed before, although many had received medical treatment for their symptoms. In Argentina, of a group of state employees (3,872 persons) who were supposed to be healthy, 263 or 6.79 per cent were found to have positive X-ray findings. Of these, 111, or 2.86 per cent, had a frankly progressive tuberculosis. In Buenos Aires, 62,349 persons were examined. Of these, 18.9 per cent showed evidence of tuberculosis; 3.08 per cent had active tuberculosis, 15.63 per cent had residual tuberculosis. It can be concluded that 5 per cent to 10 per cent, or even more, of the entire population presents X-ray or other evidence of tuberculosis. During the review of their studies the investigators found that 25 per cent of all cases who had an apparently inactive lesion, detected only by X-ray, progressed within one year. Of these, 13.7 per cent had a severe form of tuberculosis after one year. Therefore, it is advocated that even the most discrete forms of X-ray findings should be watched closely and have an X-ray film at least every three

months. In Brazil a survey was made comprising various groups of occupations with a total number of 175,277 examined persons. Amongst those, 7,824 (4.46 per cent) showed X-ray evidence of pulmonary disease; 3,821 (2.80 per cent) of the total number examined had active tuberculosis. In Uruguay, 5.62 per cent of 14,200 examined presented active tuberculosis. In Chile, 44,612 health examinations were made and 4 per cent were found to have active tuberculosis. The impression is that the primary complex in the majority of cases heals spontaneously. The same is probably true for the reinfection. It is necessary to decentralize the health service and to bring the facilities of X-ray and sputum examinations to the people, even in the smallest communities. Only in this way will it be possible to detect the tuberculous cases that are dangerous to healthy communities. In Rio de Janeiro at least 2 per cent of the population have active pulmonary tuberculosis with positive sputum. Those should be detected and sent to a sanatorium for further treatment. It is suggested that communities be built where tuberculous patients who are strong enough would have the opportunity to work and to lead a normal social life without danger of spreading the disease among healthy people. Only the very sick patients should be admitted to sanatoria or to hospitals. In the large cities only diagnostic and follow-up centres should be established, whereas the patients should be treated in rural regions.—*La pesquisa de la tuberculosis en las colectividades supuestas sanas*, M. de Abreu, *Prensa méd. argent.*, November 15, 1944, 31: 2311.—(W. Swienty)

Roentgenograms in Dispensary.—The authors studied a series of 6,700 chest X-ray films taken by the Dispensary of Nueva Pompeya; 1,074 showed evidence of pulmonary tuberculosis. Out of these, 108 (1.61 per cent) were primary infections and 976 (14.56 per cent) were reinfections. Among them were 80 (1.19 per cent) minimal, 311 (4.64 per cent) moderately advanced, and 286 (4.26 per cent) far advanced cases with sputum

positive for tubercle bacilli. The far greater part of the newly discovered cases presented moderately or far advanced tuberculosis. There were a number of cases with non-tuberculous lesions: 6 had abscess, 35 bronchiectasis, 7 emphysema, 3 hydatid cyst, 18 cancer, 8 supernumerary ribs, 10 deformities of the diaphragm, 4 diaphragmatic hernias without pneumothorax, 7 azigos lobes. Out of the 705 active cases, a pneumothorax was induced in 90 (12.8 per cent). From this number, 21 (23.3 per cent) developed fluid. It must be taken into consideration that most of these patients were ambulatory patients. The authors point out the fact that a great number of children acquire the primary infection only in the later years of adolescence. Ambulatory pneumothorax can only be given to patients in good general condition. The authors do not give any pneumothorax to patients when the disease is in progress, but wait until the acute phase is past.—*La radiografía de torax en el medio dispensarial anti-tuberculoso*, J. L. Bondi, R. Scartascina & F. A. Lamolla, *Prensa méd. argent.*, September 13, 1944 31: 1826.—(W. Swienty)

Routine Chest Roentgenography.—During a thirty-one-month period, 102,241 Negro inductees were examined. Of these, 0.83 per cent were rejected because of disqualifying tuberculous lesions, while 1.27 per cent were deferred because of the presence of small, fibrotic infiltrations. Disqualifying lung diseases other than tuberculosis were found in 0.45 per cent; the great majority of these had asymptomatic pneumonia. Miscellaneous conditions of the thoracic cage, mediastinum, pleura, diaphragm and dorsal spine were the causes for rejection in 0.28 per cent, while 0.41 per cent had abnormalities of the heart and great vessels. The comparatively low incidence of rejectable tuberculosis and high percentage of pneumonia are stressed. Ninety-four per cent of all cases were examined by means of the Army photoroentgen unit. This method, which employs 4 by 5 inch stereoscopic films, proved speedy and entirely satisfactory; supplemental films were

necessary in only 1 per cent of the cases. —*Routine Chest Roentgenography on Negro Inductees at Fort Benning, Georgia, E. R. Bowie & H. G. Jacobson, Am. J. Roentgenol., November, 1944, 52: 500.*—(P. Lowy)

Battle Injuries of Chest.—Eight cases have been selected from a large number of chest injuries recently seen. These are presented to illustrate the variety and type of pathological conditions of the chest seen in battle casualties. Two cases, one of pulmonary fat embolism and one of mediastinal emphysema, were included although there were complications of injury elsewhere. Because of the frequency of transdiaphragmatic wounds, it is preferable to examine the patient with a chest injury in upright position. If this is impossible the patient should be examined with a postero-anterior projection in the lateral recumbent position in order to detect subphrenic air. Examinations of the chest, using the portable unit and routine chest technique, are often unsatisfactory because the foreign bodies are difficult to see beneath the diaphragm or behind the heart. For this reason overpenetrated roentgenograms have often been used. Roentgenoscopy has given valuable information in many instances. The hemopneumothorax which accompanies chest injuries becomes encapsulated early due to the large amount of fibrin present. In several cases this encapsulation took place in the paramediastinal pleura and made the differential diagnosis between mediastinal pleural effusion and pericardial effusion difficult. Although some of the foreign bodies have been large and carried in bits of clothing, and although some of the injuries have been severe, no roentgen evidence of infectious processes such as empyema, lung abscess or mediastinitis has been seen. This is attributed to the early use of penicillin and chemotherapy. (Authors' Summary)—*Roentgen Pathology of the Chest in Battle Casualties, D. S. Carroll & P. Ciaglia, Am. J. Roentgenol., January, 1945, 53: 1.*—(P. Lowy)

Tuberculin Tests in Children.—In 9 per cent of the children admitted to the sanatorium the skin test was negative. In 14 out of 63 cases in which the first skin test had been negative, the second skin test turned positive. In the remaining 49 cases the allergy developed more slowly. Thirty-one children developed a positive test later. The disappearance of a previously positive skin test occurs seldom, in about 2 to 4 per cent of the cases and it stands for a bacteriological healing of the infectious focus. It is well known that allergy does not develop immediately after the entry of the bacilli into the organism, but the conception that the allergy is completed when the skin test turns positive is not always true.—*De quelques variations des réactions à la tuberculine chez l'enfant de 5 à 15 ans, Bergeron, André, Bucquoy & Beust, Rev. de la tuberc., 1941, 6: 493.*—(G. Simmons)

✓ **Vaccination with Heat-killed Tubercle Bacilli.**—Individuals in Kingston and in the rural communities of Jamaica, B.W.I., were tested with Old Tuberculin. The persons who failed to react or those who reacted only to 1 mg. of tuberculin were divided into two groups. One received a single intracutaneous injection of heat-killed tubercle bacilli. The other was left as control. About 8,000 individuals were present in each group. At the end of about 21 months between 70 and 80 per cent of both groups were examined fluoroscopically and by films for tuberculosis. Five cases of manifest tuberculosis were found in the vaccinated group and 10 in the controls. This difference, however, is not statistically significant. The authors feel that since the incidence of tuberculosis in the general population, negative or weakly positive to tuberculin, is low, the period of observation, 21 months, is too short to determine the protective value of vaccination. Furthermore, since 25 per cent of each group were not reached for observation no definite conclusions could be drawn from the findings.—*Results Obtained with Heat-killed Tubercle Bacilli Administered to Persons in a General Population, C. W. Wells & E. W.*

Flahiff, *Am. J. Hyg.*, September, 1944, 40: 109.—(M. B. Lurie)

Flahiff & H. H. Smith, *Am. J. Hyg.*, September, 1944, 40: 116.—(M. B. Lurie)

✓ **Vaccination with Heat-killed Tubercle Bacilli.**—The annual population of the Kingston Mental Hospital in Jamaica was approximately 2,500 over the past 10 years with 540 new admissions each year. Within the first 2 weeks after admission the patients were tested with tuberculin. Those not reacting to 1.0 mg. of Old Tuberculin were alternately vaccinated with heat-killed tubercle bacilli or left as controls. During the last 4 years of the 10 year period of observation the vaccine was also given to alternate patients who failed to react to 0.01 mg. of tuberculin. The vaccine was at first administered in multiple intracutaneous doses over a period of several weeks. In the latter portion of the study 0.2 to 0.3 mg. of the vaccine was given in each of two sites on a single occasion. The mortality from tuberculosis was about 65 annually. This indicates the intensity of the contagion prevalent in this institution. The tuberculosis attack and death rates were significantly lower, about one-half, among the vaccinated than among the controls, especially during the first 2 years of observation. Since the persons who received the heat-killed bacilli were not isolated from contagion following treatment it is likely that many acquired tuberculosis before adequate protection could develop from the effects of the vaccine. Nevertheless the vaccine afforded some protection under these unfavorable circumstances. The tuberculosis attack and mortality rates among persons strongly positive to tuberculin on admission were consistently and significantly lower than among persons who were weak or negative reactors to tuberculin on admission. The authors recommend the use of heat-killed vaccine as a protection for persons who may be subjected to unusual risk of tuberculous infection, for example, medical students, pupil nurses etc.—*Results Obtained in Man with the Use of a Vaccine of Heat-killed Tubercle Bacilli*, C. W. Wells, E. W.

Tuberculosis and Respiratory System.—The authors give a summary of the most important papers published during the preceding year. Several publications stress the numerical rise and the increase in the gravity of tuberculosis in all age groups. Whereas the morbidity had decreased about 50 per cent during the last twenty years, it now shows a rise of 20 to 30 per cent. Positive sputum findings in 1941 increased 290 per cent over the preceding year. Tuberculosis of the bones, too, is more frequently encountered. These observations are compared with those made during the first World War and are linked to malnutrition, lack in vitamins and physical and mental exhaustion. Several papers confirm the conception that patients with Basedow's disease offer a certain resistance to tuberculosis. Tuberculosis of the bones is most frequently encountered in the age group 2 to 6. This age corresponds to the period of an increase of the blood-flow to the bones and the transformation of cartilage into osseous tissue. These conditions facilitate deposition of bacilli in the bones, whereas the participation of the lungs is rare at this age. Pleurisy has a great importance for the subsequent development of osseous tuberculosis. In the tuberculosis of the cervical lymph nodes a fistula usually develops. In adolescents the participation of the lymph nodes in the primary infection is more pronounced than in adults. This fact is linked with anthracosis of the lymph nodes which limits the passage of bacilli. A hypertrophic form of hilar lymph node tuberculosis, resembling Hodgkin's disease, is described. Several papers deal with the importance of the blood picture for the prognosis of pulmonary tuberculosis, the importance of the sedimentation rate and of toxic granulations. Indications, technique and results obtained with Monaldi's intracavitary aspiration are described in several papers. Dumarest treated 50 cases and obtained a cure in 5. The most

important problem still remains the occlusion of the bronchus. Pneumoperitoneum is still used, in addition to a phrenic paralysis, as a substitute for a phrenic paralysis and in pulmonary hemorrhages, where the institution of a pneumothorax was not successful. The importance of vitamins in tuberculosis is dealt with in several papers, and vitamin C seems to be the most important of all. Cylindromata of the respiratory system are described in detail, the diagnosis is difficult, the clinical manifestations not being pathognomonic. In advanced cases there is extensive atelectasis. Visualization of the bronchus is essential for the diagnosis. These tumors are described as benign. In several other papers angiomata and neurinomata are described. In the therapy of asthma importance is being given to gold therapy, desensitization with tuberculin, insulin-shock therapy, prolan therapy (success in 50 per cent of cases treated) and surgical procedures.—*La tuberculose et les voies respiratoires en 1942*, P. M. Bariéty, J. Lereboullet & R. Gravois, *Paris méd.*, 1942, 1: 57.—(G. Simmons)

Posthemoptoic Pulmonary Lesions.—On the basis of experimental work done on rabbits and microscopic studies of human autoptic material the following theory concerning the pathogenesis of tuberculous lesions originating after an hemoptysis is advanced: The blood is aspirated in territories containing miliary tubercles, silent as far as the clinical and the radiological picture is concerned, and causes a perifocal reaction around these tubercles. It is this perifocal reaction which appears subsequently in X-ray films as spread of the disease.—*Sulla patogenesi delle lesioni postemoptoiche polmonari*, V. Maccone & N. Belli, *Ann. Ist. Carlo Forlanini*, 1943, 7: 64.—(G. Simmons)

✓ **Vitamin K in Hemoptysis.**—The prothrombin level was determined in 86 cases of chronic pulmonary tuberculosis. A hypoprothrombinemia, probably due to impaired intestinal absorption of vitamin K and toxic impairment of the liver functions, was found in 27 per cent

of the cases. In 10 out of 15 cases who had had hemoptysis the prothrombin was decreased. Thirty-five patients with actual hemoptysis were treated with vitamin K and in 14 a noticeable therapeutic result was observed in as far as the coagulation time was shortened and the bleeding ceased at the same time.—*Erfahrungen mit K-Vitamin bei Blut-speien*, K. F. Blom, *Svenska läk.-tidning.*, 1942, p. 639.—(G. Simmons)

Diagnosis of Apical Tuberculosis.—The evaluation of an apical tuberculosis and its activity by means of conventional X-ray films is sometimes difficult, particularly when the sputum examination and the sedimentation rate are not contributory. Tomograms are valuable in these cases because they may reveal the presence of cavities and of inflammatory changes in the bronchi which appear thickened and irregular. Two cases of apical cavities are reported, which did not appear on conventional X-ray films.—*Beitrag zur Aktivitätsdiagnose der Lungenspitzentuberculose*, A. Beckmann, *Deutsches Tuberk.-Bl.*, 1942, 16: 194.—(G. Simmons)

Adrenal Cortex and Pulmonary Tuberculosis.—On the basis of personal observation it is stated that in a great number of cases of pulmonary tuberculosis there is a coexisting hypofunction of the adrenal cortex. There is no correlation between the gravity of the pulmonary condition and the degree of adrenal dysfunction; on the contrary, insufficiency is often encountered in the initial stages of pulmonary tuberculosis, and it seems that the function of the adrenal cortex not infrequently influences considerably the course of the pulmonary tuberculosis.—*La funzionalità corticurrenale nella tubercolosi polmonare*, B. Nolli & M. Pallazoli, *Riv. di pat. e clin. d. tuberc.*, 1942, 16: 235.—(G. Simmons)

Miliary Calcifications.—Although most authors regard tuberculosis as the cause of miliary calcifications, various other etiologic agents (Aspergillus, Ascaris, oversaturation of the blood by calcium salts) have also been

suspected. The number of pathological examinations is small. The author describes the findings in 2 patients who died of causes not related to their pulmonary condition. In both cases many calcific foci were present in the lungs, together with extensive calcification in the hilar lymph nodes. The lesions were 1 to 3 mm. in diameter, yellowish white and stony hard. Careful bacteriological examination failed to reveal the presence of tubercle bacilli, fungi or any other organism. Histologically, all lesions appeared completely healed; there was central caseation and calcification, surrounded by a fibrous capsule which, in the majority of the nodules examined, showed ossification. Occasionally a few epithelioid cells, lymphocytes and plasma cells were seen. Although miliary calcifications have been reproduced in animals by the inhalation of dry mycelial spores of *Coccidioides immitis*, because of the resemblance of the lesions to Ghon tubercles and the presence of hilar lymph node involvement the author believes the condition to be healed miliary tuberculosis of the primary type. The negative tuberculin tests *in vivo* and the absence of tubercle bacilli at postmortem examination do not disprove the diagnosis of tuberculosis.—*Miliary Calcification of the Lung*, E. F. Geever, *Am. J. Roentgenol.*, June, 1943, 49: 777.—(P. Lowy)

Chronic Miliary Tuberculosis.—In 1924 Burnand and Bagé described a clinical entity characterized by the roentgenographic picture of miliary tuberculosis but with a paucity of symptoms and physical findings. The disease presents a striking contrast to the usual, acute, febrile, rapidly fatal course of miliary tuberculosis. One case is reported. The patient was a 41 year old married male whose family and past history were noncontributory. The present illness began one year before his admission to the hospital with diffuse abdominal pain occasionally severe. Two months after onset an appendectomy was done. The appendix was grossly normal but no microscopic examination was made. The roentgenogram of the chest was negative. Seven

months after onset a rectal fistula appeared. On admission to the hospital, because of abdominal discomfort, the patient looked well. Examination revealed a few râles at the left apex, abdominal distention without ascites and an anal fistula. The chest X-ray film showed miliary nodulations throughout both lungs. Examination of the fasting gastric contents revealed many tubercle bacilli. After three days the patient left the hospital against advice and returned to work. He remained more or less well with recurrent digestive complaints due presumably to disseminated tuberculous lesions.—*Granulia fria*, H. E. Osacar, *Rev. méd. d. Hosp. Ital. d. La Plata*, June, 1944, 1: 51.—(R. Kegel)

Treatment of Tuberculosis.—In initial forms of pulmonary tuberculosis and in those cases which progress favorably, the lipase content of the blood is increased, whereas it decreases as the disease becomes advanced. Since the lipolytic enzymic is bound to a protein containing ascorbic acid, it is possible to increase the lipase content of the blood by introduction of vitamin C into the blood. When the lipase values are low, the vitamin C level is low too. Vitamin C deficiency in pulmonary tuberculosis may occur because vitamin C is stored in epithelioid cells, histiocytes etc. and because of the desquamation and elimination into the alveoles of other cells filled with vitamin C.—*Probleme der Tuberkulotherapie*, B. Scholz, *Beitr. z. Klin. d. Tuberk.*, 1942, 97: 620.—(G. Simmons)

Diet in Pulmonary Tuberculosis.—The necessity for adapting the patient's diet to his instinctive desires and his condition is stressed. It was observed that patients with exudative pleurisy prefer vegetables and fruit, whereas there is a preference for meat during the process of healing of the underlying tuberculous condition. Good results are reported with the Gerson, Herrmansdorfer and Sauerbruch diet to which calcium, vitamin A, C and D had been added. Meat was given according to the desire of the patient and periodically the diet consisted for a day of

vegetables and fruit only. If this diet remains unsuccessful, the cause is seen in a "general tissural toxicosis" and the tissues must be detoxicated. This is obtained by fasting. This dietetic treatment, however, is only part of a general therapeutic scheme. Nine cases are reported.—*Beitrag zur diätetischen Therapie der Lungentuberkulose, Oefelein, Hippokrates, 1942, p. 299.*—(G. Simmons)

Diasone in Pulmonary Tuberculosis.—Thirty patients with pulmonary tuberculosis were treated with diasone (disodium formaldehyde sulfoxylate diaminodiphenylsulfone). The disease was bilateral in 29 patients, unilateral in one; it was minimal in one patient, moderately advanced in 14, far advanced in 15. All patients had active disease. Sputa or gastrics of all patients were positive for tubercle bacilli. One gram of diasone was given daily in three doses in most patients through 120 days. Cyanosis developed in 90 per cent of the cases. Other signs of toxicity were: headache, nausea, anorexia, nervousness, tremor, dizziness, vomiting. In most patients a transient anemia of moderate degree was seen. The sedimentation rate showed usually some improvement. In no case was a conversion of the sputum or gastric obtained. Chest X-ray examinations showed: diminution of exudative infiltrations in 6 cases, decrease of cavity size in 2 cases, new cavities in one case, enlargement of cavities and new infiltrations in 6 cases, no change in 15 cases. It is believed that diasone had no beneficial effect in these 30 cases.—*La diasone dans la tuberculose pulmonaire, R. Desmeules, L. Rousseau, M. Giroux & P. Richard, Laval méd., December, 1944, 9: 780.*—(G. C. Leiner)

Epituberculosis.—In 17 cases of fatal childhood tuberculosis the autopsy revealed pulmonary atelectasis. During life 13 children had shown the classical signs of epituberculosis. Atelectasis of the entire right upper lobe was found in one case, in 4 cases of parts of the right upper lobe, in 3 of the entire right middle lobe, in 4 of parts of the middle lobe,

in one of the right lower lobe, in one of parts of the left upper lobe and in three of the left lower lobe. In many cases a narrowing of the lumen of the regional bronchus was found and in all cases there were adhesions between the lymphatics and the bronchi corresponding to the atelectatic area. In 9 cases the primary focus was found in the atelectatic portion of the involved lobe, in 4 cases the primary focus was in another lobe and in 2 cases no primary focus was found. The findings seem to confirm the predominant concept that pulmonary atelectasis is the underlying anatomical lesion of epituberculosis. Atelectasis is the result of an extrinsic pressure on the regional bronchial system from peribronchial lymphatics. The lymph nodes in many cause compression and narrowing of the bronchial lumen. In a few cases inspissated caseous material resulting from perforated lymph nodes causes obstruction while in the majority of the cases adhesions between the lymph nodes and the bronchial wall seem to be sufficient to interfere with bronchial movements. This causes inflammatory and circulatory changes in the bronchial wall such as edema and congestion. Chronic atelectasis leads to collapse induration with subsequent bronchiectasis.—*Comprobacion anatomopatologica en la epituberculosis infantil, G. Llodra & A. Guzman, Arch. d. Hosp. niños Roberto del Rio, Santiago, Chile, December, 1943, 11: 149.*—(F. G. Kautz)

Epituberculosis.—The classical concept of Eliasberg's and Neuland's "epituberculosis," that is, pulmonary toxic infiltrations developing around a tuberculous focus, has been revised in recent years. The findings of Roessle in particular have demonstrated that pulmonary infiltrations of a favorable clinical course, which were classed as epituberculosis, really corresponded to atelectasis. Two hundred and forty-nine cases of this type were studied, these cases having been selected from 3,418 observations. Radiological lesions were found more often in the right upper lobe. In cases of extensive atelectasis all the known symptoms of retraction were found; in the cases of partial atelectasis, homogeneous

shadows of variable distribution were found, at times having the aspect of Sluka's triangle. Symptoms of tracheobronchial lymph node enlargement were sometimes recorded in the clinical study. Bronchoscopy could be done in 16 cases, in which tracheal and bronchial tuberculosis was found, generally of the type of congestion and edema of the mucosa, in 15 cases. The rôle of intrabronchial secretion in the production of atelectasis was demonstrated by the improvement of the radiological shadows after inspiration had been performed during bronchoscopy. In the 4 cases where autopsy was performed, tuberculosis of the tracheobronchial lymph nodes was seen, with compression of the corresponding bronchi; in all of these cases there were pathological changes in the bronchial wall itself, from edema and congestion to ulceration by lymph node bronchial perforation. The atelectasis in these cases was chronic, with phenomena of organization. The frequency of emphysema in the immediate regions of atelectasis was seen, especially on the edges of the lung.—*Estudio anatómico-clínico de las infiltraciones pulmonares benignas en la infancia*, J. Peña, E. Peña & L. Capdeville, *Ap. respir. y tuberc.* (Chile), July–September, 1944, 9: 190.—(H. Behm)

Prognosis after Pneumonectomy.—Follow-up of 25 successful pneumonectomy cases shows that the majority of patients were able to return to work. The most frequent symptom complained of was dyspnea. This was slight in 7 cases, and moderate in 2. The operations were all done for bronchiectasis or chronic suppurative diseases. It can be expected that dyspnea will be a less frequent occurrence after pneumonectomies for malignant disease because the rest of the lung can be expected to be free from abnormal conditions. The length of hospitalization and the length of invalidism before work can be started are largely determined by the absence or presence of bronchial fistula. Where no fistula developed, the average hospitalization was eleven weeks. With fistula, this was seventeen weeks. The development of fistula

did not bear any relation to the presence of dyspnea. The eventual outcome was equally good in cases with fistula as without. Development of dyspnea was more nearly related to the patient's age than to any other factor. Its incidence increased with increasing age.—*Prognosis after Successful Pneumonectomy*, J. M. Cheale & F. H. Young, *Lancet*, December 16, 1944, 247: 784.—(H. Marcus)

Lung Abscess and Tuberculosis.—The co-existence of tuberculosis and a lung abscess is not as unusual as is generally believed. Five cases of putrid abscess superimposed on the course of a chronic cavitary pulmonary tuberculosis are reported. This complication affected the clinical course, death resulting in 4 cases. Autopsy showed the existence of a superimposed acute inflammation on the wall tuberculous cavities in 2 cases. Three cases of pulmonary abscess were also found in which tubercle bacilli were occasionally found in smears of the sputum. In spite of this finding the abscess continued its normal course and clinical tuberculosis was not found during the period of observation. These cases have been explained by assuming that the abscess destroys an old tuberculous focus, freeing tubercle bacilli and eliminating them through expectoration.—*Supuraciones pulmonares en tuberculosos*, E. P. Aznarez, *An. d. fisiol. y climatol.*, 1943, 2: 3.—(H. Behm)

✓ **Diabetes and Tuberculosis.**—Twenty-nine cases of diabetes with tuberculosis have been studied. Ninety-four per cent of the cases occurred between the ages of 30 to 60 years. Most of the lesions were located in the perihilar region, 13 of which were of a mixed type, 3 of the fibrotic and 10 of the exudative type. There were 3 caseous pneumonias and in 70 per cent cavitation was present. All cases were already in an advanced stage when admitted to the sanatorium. Hemoptysis, pleural effusion and laryngeal involvement were more frequent and the prognosis was definitely worse than amongst the nondiabetics with similar tuberculous lesions. The death rate was 20 per cent in the combined disease group

as compared to 10 per cent among the non-diabetics. There were 2 deaths directly due to hemoptysis and both occurred among the diabetics. The antidiabetic treatment consisted of a standardized diet of about 2,500 calories with a generous allowance of protein and high carbohydrates in addition to insulin which was given up to one hundred units per day without any apparent ill-effect. Insulin was not given while the patient was bleeding. The antituberculous treatment consisted of collapse therapy, gold injections and sanatorium care. Improvement occurred in the diabetics in 44 per cent as against 58 per cent in the nondiabetics.—*Diabetes and Tuberculosis*, M. P. Sinha, *Patna J. Med.*, January, 1944, 19: 1.—(F. G. Kautz)

Diabetes and Tuberculosis.—An analysis of the reports of ten American clinicians based on the observations of 17,358 cases of diabetes indicates a higher incidence of tuberculosis in diabetic persons than in the general population of the United States. The increased susceptibility of diabetic patients to tuberculosis is probably due to several causes, of which vitamin-A deficiency is considered the most important. The number of patients with diabetes and pulmonary tuberculosis treated in specialized institutions is far below the estimated number of tuberculous diabetic persons. The conception that asymptomatic tuberculosis is a characteristic complication of diabetes is untenable; this type of pulmonary tuberculosis has often been found in roentgen ray surveys of nondiabetic patients. For the recognition of early tuberculosis, all diabetic patients should be tested with tuberculin and the test should be repeated periodically on all patients with negative reactions to tuberculin. A roentgenogram of the chest should be taken for all patients with positive reactions at least once a year. Adequate search for tubercle bacilli should be carried out when sputum is available or when roentgenologic observations justify repeated aspirations of the fasting gastric contents. Of the 125 diabetic patients admitted to Muirdale Sanatorium between January 1, 1923 and December 31, 1943, only

3 (2.4 per cent) had minimal and 104 (83.2 per cent) had far advanced pulmonary tuberculosis. Spontaneous pneumothorax occurred in 8 patients (6.4 per cent). The results in diabetic patients who, under a well planned diet and adequate amounts of insulin, showed slight glycosuria and hyperglycemia not exceeding 200 mg. per cent compare favorably with those in tuberculous patients whose blood sugar was maintained on a normal level. The administration of massive doses of vitamin A is advised. Indications and contraindications for collapse therapy are the same for diabetic as for nondiabetic patients. One hundred and fifteen diabetic tuberculous patients were discharged from the sanatorium during the observation period. Of the persons with moderately advanced pulmonary tuberculosis, 47 per cent were classified as having the disease apparently arrested, quiescent or improved, and 53 per cent were unimproved or had died. Of the far advanced group 14.5 per cent were apparently arrested, quiescent or improved, while 85.5 per cent remained unimproved or died. These therapeutic results are less favorable than those recorded for nondiabetic patients with moderately advanced and far advanced pulmonary tuberculosis.—*Diabetes and Tuberculosis*, A. L. Banyai & A. V. Cadden, *Arch. Int. Med.*, December, 1944, 74: 445.—(G. C. Leiner)

Jaundice and Tuberculosis.—On the basis of 16 cases reported in this paper the author arrives at the conclusion that catarrhal jaundice always influences tuberculosis unfavorably.—*Katarrhalische Gelbsucht und Lungentuberkulose*, F. Pongor, *Beitr. z. Klin. d. Tuberk.*, 1942, 97: 603.—(G. Simmons)

Fatty Liver in Tuberculosis.—Three case reports are presented of patients with pulmonary tuberculosis who showed an enlarged, painless liver of boggy consistency with smooth, rounded edges. The prominent symptoms were anorexia and weakness. At autopsy fatty infiltration of the liver was found. Autopsy material was studied from 581 tuberculous patients. Fatty infiltration

of the liver was present in 244 cases (41.9 per cent). Amyloidosis was present in 37 cases (6.3 per cent). Three hundred and ten cases (53.3 per cent) had intestinal tuberculosis. Extensive fatty infiltration of the liver was often associated with extensive tuberculous enteritis. Fatty liver was found frequently in patients with tuberculous enteritis, when the accompanying pulmonary disease was exudative or "mixed" (exudative and proliferative). Patients with fatty liver usually showed extreme emaciation.—*Incidence of Fatty Liver in Tuberculosis with Special Reference to Tuberculous Enteritis, Julia M. Jones & W. M. Peck, Arch. Int. Med., November, 1944, 74: 371.*—(G. C. Leiner)

Hydatid Cyst and Tuberculosis.—The co-existence of hydatid cyst and pulmonary tuberculosis is relatively infrequent. About 3 per cent of the cases of pulmonary echinococcus disease are complicated by pulmonary tuberculosis. The author presents one case in which tuberculosis was found as complication after operation for echinococcus cyst of the lung. The diagnosis of hydatid cyst was made by a positive Cassoni test and X-ray findings. The cyst was removed by thoracotomy and the patient was discharged with a small hydropneumothorax on the operated side. He reentered shortly afterwards with tension pneumothorax, cough and fever. His sputum was free of acid-fast bacilli, but in the exudate many tubercle bacilli were found. The patient died of miliary tuberculosis. A tuberculous infection prior to the operation evidently caused the spread. There are four possibilities of coexistence of hydatid cyst and tuberculosis: (1) tuberculosis of the lung and echinococcus disease in other parts of the body; (2) pulmonary tuberculosis and hydatid cyst of the lung; (3) echinococcus disease of the lung cured either by surgery or by spontaneous emesis which later presents an active tuberculous lesion in the scar or in the residual cavity; (4) sudden outbreak of acute tuberculosis, probably of the miliary type, after operation for hydatid cyst.—*Hidatidosis y tubercu-*

losis pulmonar, C. I. Rivas, Rev. Asoc. méd. argent., May 30, 1944, 58: 331.—(W. Swienty)

✓ **Amebiasis and Tuberculosis.**—Pulmonary tuberculosis results, beside other factors, from a lowering of the systemic resistance. This resistance in turn depends much on the power of digestion and of the assimilation and absorption of food material from the intestinal tract. The author reports 3 cases, one of unilateral and 2 of bilateral pulmonary tuberculosis associated with chronic intestinal amebiasis. All 3 cases were hospitalized but in spite of an adequate antituberculous treatment they showed poor appetite and failed to gain weight and to respond favorably to the treatment. Only after the discovery and cure of the associated amebiasis, appetite, digestion and assimilation were definitely improved. And after reaching this stage the patients recovered in due time. The author emphasizes the great importance of ascertaining and treating the cause of failure of food assimilation and thus of ensuring a turn to recovery.—*Certain Aspects in the Treatment of Pulmonary Tuberculosis, D. R. Dhar, Indian M. Rec., May, 1944, 69: 5.*—(F. G. Kautz)

Miliary Tuberculosis and Chronic Colitis.—A 23 year old female patient had symptoms of ulcerative colitis for about one year. Ileostomy was performed eight months later, but she did not improve. She developed chest pain and a small amount of sputum which was negative for tubercle bacilli. She had persistent hemorrhages by rectum and severe abdominal pain. X-ray films of the chest showed consolidation of most of the right lung, with cavity, and miliary disease throughout the remainder of the lungs. There was splenic enlargement, evidence of liver damage and clubbed fingers. She also had rheumatic heart disease. Autopsy showed pulmonary tuberculosis and miliary tuberculosis of all organs, together with tuberculous peritonitis without ascites. She had chronic ulcerative colitis which was typical and apparently unrelated to the tuberculous process.—*Case Record of the Massachusetts General Hospital,*

Case 30522, *New England J. Med.*, December 28, 1944, 231: 890.—(H. Marcus)

Subclavio-Phrenic Nerve.—This is a rare anatomical condition and found in only 1 per cent of all autopsies, but it is of great importance if a phrenicoexeresis results in failure to collapse the diaphragm. In this case, the substitution of the phrenic by the subclavian nerve has to be suspected. Four cases are described. In the first one, the subclavian nerve took over the rôle of the phrenic with all its branches. It received only a small filament from the fourth cervical segment. In 2 other cases there was no phrenic nerve at all and in the last case the phrenic and the subclavian nerves ran parallel and had an equal distribution of their branches.—*El nervio subclavio-frenico*, A. P. Belou & C. Capdevila, *Rev. Asoc. méd. argent.*, September 30, 1944, 58: 825.—(W. Swienty)

Respiratory Function in Pneumothorax.—The respiratory function was studied in 29 cases of monolateral and 12 cases of bilateral pneumothorax. Spirometric studies were made first with atmospheric air, then with pure oxygen; after one minute of exercise and again after ten minutes' rest following the exercise, the spirometric readings were repeated. The respiratory rate, the tidal air, the minute volume and the oxygen consumption per minute were recorded; furthermore the rate of the oxygen debt was calculated. The relative oxygen debt rate was obtained by comparing the oxygen consumption at rest and after exercise. Finally the maximum ventilation per minute was determined by making the patient breathe as deeply and as frequently as possible for about ninety seconds. The difference between the minute volume and the maximum ventilation per minute is considered the respiratory reserve. Respiratory insufficiency was diagnosed when the relative oxygen debt was above 25 per cent. Adopting this criterion, respiratory insufficiency was diagnosed in 18 cases out of 29 cases of unilateral pneumothorax (62.06 per cent) and in 6 cases out of 12 cases of bilateral

pneumothorax (50 per cent). There was no definite evidence of a direct causal relationship between the extent and the type of lesions, the type and the degree of collapse and the respiratory insufficiency. It was noteworthy that the minute volume, ten minutes after exertion, remained above 1,000 cc. more often in cases with respiratory insufficiency than in those without respiratory insufficiency. The higher percentage of respiratory insufficiency in cases with unilateral pneumothorax may be due to the major performance of work.—*Estudio de la función respiratoria en los tuberculosos pulmonares tratados por el neumotorax artificial*, J. B. Rocca, *Temas Tisiol*, Cordoba, September, 1943, 176: 189.—(L. Molnar)

Atelectasis in Pneumothorax.—Reference is made to a previous paper dealing with the same subject. The cortical atelectasis in the course of pneumothorax treatment seems to occur more often and more readily at high altitudes, as for instance in the town of Potosi, 4,000 meters above sea level. An attempt is made to explain this phenomenon. The processes regulating the pressures, and the diffusion in the gaseous exchanges in general, are also contributing in the mechanism of atelectasis. With the diminution of the atmospheric pressure in high altitudes, the gaseous exchanges are reduced and so is the oxygen dissolved in the blood plasma. In the case of miners, there is also hypoventilation in the mines; the inhalation of dust also impairs the hematosis. The increased oxygen requirement under these conditions may also produce a loss of intraalveolar oxygen. The increase in weight of silicotic lungs may also be an important factor. All the above mentioned factors may play their rôle also at sea level, but their influence is greater at high altitude. Certain histological features of the cortical areas of the lungs, such as reduced thickness of the lung tissue, the easy obstruction of the terminal bronchioli, predispose these areas for the production of atelectasis.—*Estudios de prosecucion de las atelectasias de los bordes pulmonares, en el curso del neumotorax*

terapeutico, llevados a cabo en la Ciudad de Potosi, R. A. Subieta, *Ap. respir. y tuberc.* (La Paz), No. 15-16, 1943, 86: 90.—(L. Molnar)

Intrapleural Pneumonolysis in Children.—The authors started to perform the operation of Jacobaeus in children in 1938. The indications were at first strictly limited to cases with open cavity and positive sputum. Later all cases were included showing adhesions on X-ray films even without evidence of cavitation. The operation of Jacobaeus was performed in 113 cases: 48 boys and 65 girls; 13 cases from 9 to 12 years, 45 cases from 13 to 15 years, 55 cases from 16 to 18 years. No narcotics were given preoperatively. It was noted that children behaved much more quietly on the operating table than adults. The authors are in favor of early pneumonolysis (five to six weeks after induction of pneumothorax). Of 84 pneumonolyses, 49 were complete and 35 partial. Of the 49 patients who underwent complete pneumonolysis, open cavity had been present in 29 cases, positive sputum in 24 cases. After pneumonolysis the cavity disappeared in 20 cases (69 per cent); it was markedly diminished in 5 cases and unchanged in 4 cases. The sputum converted in 70 per cent of cases. After partial pneumonolysis the cavity disappeared in 53 per cent of cases. The sputum converted only in 9 out of 20 cases. Fluid collections in the costophrenic angle following operation were observed in 33 cases (29 per cent), effusions reaching the eighth ribs in 5 cases and massive effusion with fever in 2 cases. The authors conclude that there is no reason for reserve in the application of pneumonolysis in children, this operation being well tolerated and not giving a higher incidence of complications than in adults.—*The Operation of Jacobaeus in Children and Adolescents*, A. O. Majanz & F. I. Braginskaja, *Probl. tuberk.*, 1944, 4: 25.—(V. K. Leites)

Extrapleural Pneumothorax.—The authors give further information on a previous report of the results of extrapleural pneumothorax in

the treatment of pulmonary tuberculosis. They detail the late results in 32 cases operated between 1938 and 1940. The immediate results were successful in 46 per cent of the cases (first report). The late good results dropped to 31 per cent (second report). Empyema was observed in 10 cases, 4 of which died. Complementary thoracoplasty used in those cases where extrapleural pneumothorax was ineffective, presented great technical difficulties and proved to be ineffective in many cases. In view of this result the authors have become more skeptical. They recommend, therefore, to give up this method and replace it by a thoracoplasty following a rest cure which may allow stabilization of lesions.—*Neumotorax extrapleural (Resultados alejados)*, *Medicos del Hospital-Sanatorio "El Peral," Bol. d. Hosp. San. "El Peral," April, 1944, 4: 37.*—(H. Behm)

Extrapleural Pneumothorax.—This paper deals with the problem of the maintenance of extrapleural pneumothorax with highly positive pressures with the view of preventing obliteration of the extrapleural space. The study is based on 30 cases operated upon in the surgical service of the Moscow Institut for Tuberculosis from 1938 to 1943. At first the authors employed highly positive pressures in the very early postoperative period. The pressures exceeded those indicated on the manometer of the usual pneumothorax apparatus (40 cm. water) and were consequently administered with exclusion of the manometer. This procedure was later recognized to be erroneous. The high pressures produced a disruption of the still unconsolidated wound and a leakage of the extrapleural space with occurrence of massive emphysema and perforation of the extrapleural fluid through the opening. In all these cases there was a rapid loss of the extrapleural space. In subsequent cases the extrapleural pneumothorax was carried on under a more cautious regimen with slower increase in pressures during the first postoperative month and the use of high pressures under exclusion of the manometer only from the second postoperative month on or

later. The authors claim that this policy was successful in the majority of the remaining cases and that, with the exception of cases complicated by empyema, they had no instances where the progressive diminution of the extrapleural space could not be counteracted by high pressures. It is furthermore emphasized that the use of such pressures from the second month on have not led to serious complications. A common complaint after the refill was the sensation of a slight and transient oppression in the chest. Only a few cases showed pain in the arm, precordial pain, sudden headache and short fainting spells. These phenomena are attributed to high pressure on the vessels and nerves of the exposed mediastinum. It was observed that an elevation of the axillary temperature on the homolateral side was a very frequent occurrence. In 1943 the authors inserted a mercury-manometer into their pneumothorax apparatus. Readings taken in extrapleural pneumothoraces conducted in the above described way revealed the commonly employed pressures to be between +60 and +80 mm. mercury. In some cases with a small extrapleural space and not exposed mediastinum the final readings were +150 mm. mercury and higher. The sensations of the patient during and after the refill, the X-ray follow-up of the obtained collapse, and sputum examinations were the main criteria in establishing the regimen of extrapleural pneumothorax. It is stated that extrapleural pneumothorax conducted with high pressures does not considerably diminish respiratory function. In conclusion, the question is brought up whether such high pressures do not lead to inexpandable lung. The authors count with this possibility but do not believe that the other alternative of conserving the extrapleural space, namely extrapleural oleothorax, guarantees in a larger measure the reëxpansion of the lung. The opinion is expressed that fundamentally the application on a large scale of extrapleural pneumothorax has already converted this intervention to a permanent collapse procedure. A life-time continuation of this form

of collapse is advocated and it is believed that in this way the indications for thoracoplasty might be reduced.—*The Regimen of Extrapleural Pneumothorax*, D. S. Kvachnin, *Probl. tuberk.*, 1944, 3: 33.—(V. K. Leites)

Extrapleural Pneumonolysis.—Difficulties in the management of extrapleural pneumonolysis do not consist in the operative technique but in the great number of possible postoperative complications. It was observed that those cases in which the tuberculosis had not become stabilized the procedure was followed by a more profuse exudation. The inflamed and richly vascularized pleura reacts with hemorrhages, whereas cases in which there are productive processes with a thickened pleura remain dry. The greatest danger consists in the subsequent contamination of the extrapleural exudate. To minimize all these complications, the patients have to be well chosen; cases with exudative not yet stabilized processes have to be eliminated. Calcium and vitamin C are given preoperatively. Careful hemostasis must be done and the operation should be as short as possible. Cortical cavities should not be touched. Aspiration of the exudate should be avoided during the first eight postoperative days, if possible. Absolutely sterile technique is essential. The results obtained with lavage depend primarily on the nature and virulence of the infecting organism and upon the resistance of the body and only secondarily on the antiseptic properties of the solution used. Prolonged lavage often influences the general condition of the patient unfavorably and decreases the patient's resistance. Better results are obtained with the drainage as advocated by Monaldi. The exudate is being drained daily and substituted with air. Finally the extrapleural space is filled with paraffin and the fistula closes. In the presence of a bronchopleural fistula and secondary infection of the extrapleural space a secondary thoracoplasty is essential. It is important to maintain the extrapleural pneumothorax long enough to obtain arrest of the underlying pulmonary condition and yet to abandon it

before the walls of such a pneumothorax become rigid. Such spaces always fill with exudate and, should a thoracoplasty become necessary later on, the result will not be as good as would have been obtained over an extrapleural pneumothorax with elastic walls. —*Komplikationen und Nachbehandlung der Pneumolyse*, A. Emmeler, *Deutsches Tuberk.-Bl.*, 1942, 16: 146.—(G. Simmons)

Thoracoplasty.—The cases referred to in this paper correspond to 122 patients who were treated for pulmonary tuberculosis by thoracoplasty, 67 of whom were males and 55 females, the age ranging from 16 to 52, averaging 27. Up to the moment of the operation, the average age of the lesion was 30.4 months. Twenty-three months of duration before sanatorium treatment correspond to 6.5 months of active work done after diagnosis or between periods of treatment; 11.5 months of rest at home and 5 months of hospitalization not in the sanatorium. It was noted that males work for a longer period (10 months as an average) than females and that they stay hospitalized for shorter periods (4 months). Up to the moment of the operation each patient represents a cost of US \$800, without taking into account the cost of previous ambulatory treatment and the industrial working hours lost in this period. The cost of each surgical recovery estimated in the same way amounts to US \$400. The lesions presented by these patients were 101 cavitory lesions (63 cases with cavities up to 2 cm. in diameter, 19 cases with cavities 2 to 5 cm. in diameter and 19 cases with cavities above 5 cm.); 13 predominant infiltrative lesions and 8 tuberculous empyemata. The successful results, (including cured, apparently cured, arrested, apparently arrested and quiescent lesions) as investigated more strictly than those stated in the National Tuberculosis Association standards (8 cultures of gastric lavage being the average employed in this investigation), were as follows: 69 per cent in cavitory lesions, 92 per cent in predominant infiltrative lesions and 50 per cent in empyemata. In the cavitory cases, the lower

the cavity the less successful were the results. The same applies for anterior and internal cavities. Also, the larger the cavities, regardless of their location, the less effective is the operation. Generally speaking, the results of the treatment varies according to extension and age of the lesions. Out of the lesions occupying one-third of the lung, 32 per cent were at least 24 months old; 75 per cent of the complicated and bilateral lesions were also included in the group of a greater age. Seventy per cent of the cases under 19 months of duration showed favorable results as compared with 60 per cent in cases of older lesions. Eighty of the 122 patients were operated at the Surgical Department of the Hospital-Sanatorio "El Peral" and 42 at the Surgical Unit of the Hospital "San Jose." of those operated at the Hospital-Sanatorio "El Peral," 72 per cent showed favorable results; of the entire group of 122 patients, 64.7 per cent showed favorable results. Mortality, either immediate or later, was 13.7 per cent for our patients and 17 per cent for the whole group. The period between the end of the surgical treatment and the last clinical control is 9.5 months on the average. The lapse of time between the last clinical control and the date of this study averaged 3.6 months.—*Toracoplastia en el tratamiento de la tuberculosis pulmonar*, *Medicos del Hospital-Sanatorio "El Peral," Bol. d. Hosp.-San. "El Peral,"* October, 1944, 4: 102.—(H. Behm)

Collapse Therapy for Apical Cavities.—The results obtained by different types of collapse therapy in the treatment of 73 apical cavitory pulmonary tuberculosis have been studied. The purpose of this study was to verify the statement made by Coryllos that thoracoplasty is to be preferred in the treatment of this kind of lesions. The conclusions are: (1) Apical cavitory tuberculosis should not be treated by pneumothorax, which is often an ineffective treatment, implying a high proportion of complications. (2) In the 73 cases reported, pneumothorax was effective only in 5.7 per cent of the patients on whom it

was attempted and only in 13 per cent of the cases where the pleural space was found free. In the unselected cases of pulmonary tuberculosis the corresponding percentages are 49 per cent and 68 per cent. (3) The frequency of a serious inflammatory pleural effusion which impedes continuing the pneumothorax was 26 per cent which is very high when compared with similar complications in nonselected cases of pneumothorax, which amount to 4.7 per cent. (4) The failure of pneumothorax in these cases is due to the fact that the cavity is located in the pulmonary region of shortest diameter, which results in a rapid pleural involvement. This fact is demonstrated by (1) The high percentage of failures in the first attempt to create a pneumothorax (25 per cent); (2) the observation that every pneumothorax brought about had pleural adhesions, and (3) the low proportion of complete division of adhesions (26 per cent) in the cases where pneumonolysis was attempted. This operation became complicated in 8.7 per cent of the cases with empyema. (5) It is emphasized that apical cavitary tuberculosis are primary indications of thoracoplasty, which is the type of collapse that gives best results in these cases. In the 14 cases operated on, 10 were successful (roentgenological cavity closure, persistent sputum conversion in cultures). The operation should be postponed only when a preoperative stabilization of lesions is indicated. (6) There are but two exceptions to this rule: (1) bilateral apical cavitary tuberculosis and (2) unilateral apical cavitary tuberculosis which are progressive when on rest-cure and which extended down to the infraclavicular region. In both cases, attempts to create a pneumothorax are accepted, for lack of any better method, provided that (1) mechanical effectiveness is obtained within a period of six to eight weeks, and (2) bacteriological and roentgenological effectiveness be obtained within two months following pneumonolysis. (7) For the application of the foregoing conclusions by apical cavity is understood a cavity the major portion of which is projected in the roentgenogram in the region limited by the mediastinum

inwards, the internal border of the first rib upwards and outwards and by a horizontal line passing along the inner border of the first rib at the level of the chondrocostal junction, downwards.—*Colapsotepia de las cavernas apicales, Medicos del Hospital-Sanatorio "El Peral," Bol. d. Hosp.-San. "El Peral," April, 1944, 4: 5.*—(H. Behm)

Revisión Thoracoplasty for Residual Cavities.—Thoracoplasties performed by the author are usually done in three stages. The upper three ribs are taken out completely with their cartilages and with the corresponding transverse processes, and of the lower ribs as much is removed as is necessary to obtain a good collapse and the sinking-in of the scapula. An apicolysis, as complete as possible, is added. The results thus obtained are usually good, but sometimes residual cavities persist because of insufficient rib resection, too prolonged intervals between stages or too advanced fibrous induration of the lung. In this case a revision operation is done, which consists of an additional plastic operation and a muscle plombage. The procedure is carried out in two stages. During the first stage, through a posterior incision, residual pieces of ribs and transverse processes are removed and the lung is separated from the costovertebral gutter as much as possible. After one to two weeks the second stage is performed. This time the incision is made parallel to the clavicle and then extended downward along the sternal border. The skin is separated and the clavicular and sternal portion of the pectoral muscle is separated by blunt dissection, as far back as to the humerus, where the insertion of the sternocostal portion is cut. The sternal insertion of the pectoral remains in situ in order to maintain the mammary artery intact. Thus, after dissection of the pectoral, remains of ribs and cartilages can be resected. Then a parasternal incision through the costal perichondrium and the intercostal muscles is made until the pleura is met, where the lung is separated bluntly from the thoracic wall and from the mediastinum as far as possible.

Following hemostasis the dissected portion of the pectoral muscle is placed into the extra-pleural space thus created and sutured in the region of the transverse processes. The muscle is supposed not only to fill the space thus created but also to form a firm wall, extending from the sternum to the costo-vertebral gutter. Five patients were operated on according to this technique and the operation was well tolerated. Cure was obtained in 3, one had a contralateral spread and one developed intestinal tuberculosis. In both these cases a small residual cavity had persisted.—*Über die Korrektionsplastik bei Restkavernen*, O. Hultén, *Acta chir. Scandinav.*, 1942, 86: 315.—(G. Simmons)

Thoracoplasty.—A new technique of thoracoplasty is described. An incision is made near the posterior border of the sternocleidomastoid muscle towards the acromio-clavicular articulation. The first rib is visualized, the periosteum incised in H form and stripped for 1.5 cm. Then a special raspatory with a long, graduated elastic handle is introduced and the rib freed from the periosteum subperiosteally. A specially constructed saw which also cuts subperiosteally is then inserted and the whole of the rib resected. The second rib is approached through the same incision and also resected entirely. It may be necessary to do a counter-incision just below the clavicle if it is not possible to reach the end of the rib and the transverse process by the first incision. The third, fourth and fifth ribs are approached by an incision one and one half inches long and in line with the middle of the fourth rib. Here, also, an H incision is made in the periosteum and the same technique used as previously described. The other ribs are approached in a similar way. This operation has distinct advantages: Injury to the tissues is minimal. The absence of an extensive incision reduces the dead space in which abscess formation is possible. The danger of postoperative infections is minimal. There is very little loss of blood. The action of all muscles is maintained. The technique

is easy. The operation can be done in a very short time and there are no residual deformations.—*Toracoplastia anatomica (communicacion previa)*, M. C. Bortagaray, *Rev. Asoc. méd. argent.*, May 15, 1944, 58: 300.—(W. Swienty)

Surgical Treatment of Cavities.—In the attempts to improve the technique of thoracoplasty two features of the tuberculous cavity were not sufficiently considered: (1) the cavity wall, (2) the draining bronchus. In rigid cavities thoracoplasty in itself is not sufficient to cause a decrease in size of the cavity, but a considerable difference between the pressure inside the cavity and the pressure from the outside is necessary to obtain a shrinkage. This difference in pressure can be obtained either by decreasing the inner pressure by means of an intracavitary aspiration or by increasing the outer pressure. Kinking of a bronchus with consequent formation of a bronchial valve-mechanism leading to the ballooning of the cavity is a frequent occurrence after a thoracoplasty. In this case too, intracavitary aspiration can produce good results. Best results, however, are obtained when intracavitary aspiration is employed prior to performance of the thoracoplasty instead of later when the results obtained surgically appear to be unsatisfactory. This thesis is proved on the basis of 3 reported cases, in which big cavities were present and the general condition of the patients were so bad that a surgical procedure could not be considered. After institution of the cavitory drainage the general condition improved, the cavities shrank and a subsequent thoracoplasty gave good results. The presence of the catheter complicates the operative procedure, but the author believes that nevertheless intracavitary aspiration with following thoracoplasty should be the procedure of choice in big, rigid-walled cavities.—*Neue Gesichtspunkte bei der chirurgischen Behandlung der tuberkulösen Kaverne*, A. Brunner, *Deutsche Ztschr. f. Chir.*, 1942, 255: 417.—(G. Simmons)

Intracavitary Aspiration.—Experiences with 17 cases of cavity aspiration are summarized. In 15 cases the cavities corresponded to Pinner's type II, the other 2 were classified as type III; in the latter the indication for aspiration treatment was considered poor. In general, Monaldi treatment is most indicated in thin-walled balloon cavities located in the upper lobe and accessible to anterior approach; there should be no lobar atelectasis, no other cavities, and the disease should be relatively recent. Every available method should be utilized for the accurate localization of the cavity. Within a few days after institution of drainage the cavity shows marked decrease in size. There is an increase in the density surrounding the cavity; after several months the density gradually absorbs. Opposite the cavity the pleura becomes thickened and remains so. The distance between the cavity and the chest wall increases, apparently confirming Monaldi assumption of atelectasis around the cavity. As the cavity becomes smaller and flatter, tomography is needed to visualize it. The state of the tract between the cavity and the chest wall is also best determined by tomography. In 10 out of the 17 cases reviewed the cavity persisted after Monaldi's aspiration.—*Roentgenographic Aspects of Monaldi's Cavity Aspiration in Pulmonary Tuberculosis*, W. R. Oechsli & E. Kupka, *Am. J. Roentgenol.*, December, 1948, 50: 733.—(P. Lowy)

Intracavitary Aspiration.—The old conception of the delimitation of caseous foci by a capsule composed of newly formed connective tissue cannot be accepted any longer. The author believes that such a delimitation occurs rather on the basis of physico-chemical phenomena, such as acidification, dehydration, flocculation of colloidal substances and precipitation of minerals, decomposition of fatty acids etc. Such complex chemical changes in turn determine fixation of bacilli, make it impossible for the associated bacterial flora to develop; they lead to an alteration of the normal humoral exchanges and the absorption of such complex materials becomes impossible.

A cavity thus delimited becomes, biologically, a separate entity. These cavities are called "cavities, biologically limited." Then there are the "fusion cavities," in which the loss of substance is due to coalescence of caseous foci. The pathological material remains semifluid and the humoral exchange remains active. Between these two extremes there are (1) cavities in the process of delimitation and (2) cavities that can be limited, but are not limited yet for different reasons (insufficient drainage of pathological material, persistence of a perifocal exudation etc.). Intracavitary aspiration is not feasible and may be dangerous in "fusion cavities." Monaldi's procedure can be applied successfully only in cavities in which the loss of substance was not great and it is necessary to study in retrospect the history of the cavity, to determine whether it originated from the fusion of several caseous foci (great loss of substance) or from a centrifugal extension of one focus (relatively small loss).—*Il campo di applicazione dell'aspirazione endocavitaria (Direttive generali)*, V. Monaldi, *Boll. e Atti d. Acc. di Roma*, 1943, vol. 49.—(G. Simmons)

Intracavitary Aspiration.—Over a period of two and one half years 40 patients with pulmonary tuberculosis were treated with the intracavitary aspiration as advocated by Monaldi. The best indication is an isolated stable cavity of the upper lobe without considerable peripheral infiltration. It is dangerous to aspirate cavities located near the hilum. In the majority of cases the success, characterized by decrease of cough and sputum, manifests itself immediately after institution of Monaldi's procedure, and the general condition of the patient improves. By means of lipiodol the progressive obliteration of the draining bronchus could be demonstrated. Out of 40 cases the drainage was unsuccessful in 15 because the disease was already too far advanced; 2 patients died of postoperative hemorrhage. In 7 cases only partial results were obtained; 5 cases or 12.5 per cent were completely cured. In these cases aspiration was carried on for a variable

period of eight to twenty months. All these "cured" cases had apical cavities. In all cases the catheter was eliminated spontaneously. In 11 cases aspiration and thoracoplasty were combined, drainage being performed before thoracoplasty in the majority of cases. In 2 cases intracavitary aspiration of a cavity persistent after a thoracoplasty was done and in one of these cases the result was good.—*Deux ans d'expérience du drainage endocavitaire*, F. Dumarest, P. Brette & J. Germain, *Presse méd.*, 1942, 37: 373.—(G. Simmons)

Reconditioning after Chest Surgery.—A reconditioning program consists of physical reconditioning, educational reconditioning, occupational therapy and recreation. The specific problems of a reconditioning program for patients convalescing from a surgical disease of the chest are a lowered vital capacity, a decrease in stamina and strength, postural defects and the loss of power of large muscle groups. The rehabilitation of the tuberculous patient takes place following discharge from the Army. The reconditioning program for patients with suppurative thoracic disease lasts from ten days to two weeks. The patient returns to the hospital for dressings but otherwise he is removed from the hospital atmosphere and is engaged in graded exercises such as breathing exercises, calisthenics, outdoor drills and marches. Vigorous physical activities has been found of benefit in hastening the obliteration of empyema and lung abscess cavities. Of 22 patients with chronic nontuberculous empyema 18 were returned to duty. If pulmonary resection is necessary the patient will usually be able to return to duty if no more tissue is resected than the amount contained in the middle and lower lobes of the right lung. The period of immediate convalescent care is followed by a period of physical therapy which extends from the seventh to the twenty-first postoperative day. The therapy consists of breathing exercises and shoulder exercises given twice daily. They may be supplemented by local application of radiant heat or general application of ultra-

violet irradiation. After the third week the patient is transferred to the Reconditioning Service where he undergoes the same routine as the patient recovering from a suppurative pulmonary disease. Swimming was found of particular value for patients recovering from pulmonary resection. The average length of hospitalization was about ten weeks. Of 31 patients treated by resection, 25 were returned to duty, 3 were discharged because of suppurative sinus disease and suppurative bronchitis, 3 were discharged for reasons not related to the pulmonary condition. Patients who required exploratory thoracotomy followed the same routine with good result.—*Reconditioning in Chest Surgery*, J. B. Grow, O. M. Raines & O. L. Huddleston, *J. A. M. A.*, December 23, 1944, 126: 1059.—(H. Abeles)

✓ **Costa Reaction.**—The diagnostic and prognostic value of the reaction was investigated. The test, as standardized by the author, is performed as follows: 0.2 cc. of blood is added to 1.5 cc. of 2 per cent procaine in 0.85 per cent saline, the mixture centrifuged for five to eight minutes, and then one drop of formalin added. A positive reaction is indicated by the appearance of a distinct cloud within three to ten minutes. The results were graded according to the time of the appearance of the cloud. The test was negative in 25 normal individuals, positive in 88 per cent of the 140 cases of pulmonary tuberculosis tested. The reaction is of no value in the diagnosis and differential diagnosis of pulmonary tuberculosis, since it is frequently negative in definitely diagnosed early cases and, on the other hand, it is often positive in other intrathoracic conditions, including heart diseases. It can, however, be used to determine the progress of pulmonary tuberculosis; progressively stronger reactions indicate increasing activity of the disease, while improvement is usually associated with weakening reactions. The nature of the reaction is not known.—*The Costa Reaction: A Simple Test for Assessing the Progress of Pulmonary Tuberculosis*, S. Cohen, *South African J. M. Sc.*, May, 1944, 9: 59.—(P. Lowy)

Pulmonary Lavage.—Bacteriologic examination of sputum and gastric contents in the usual manner is not always satisfactory in the diagnosis of active pulmonary tuberculosis. Many patients do not expectorate, although they have suspicious X-ray findings. On the other hand, tubercle bacilli will not be found in a smear unless their concentration is 100,000 or more in 1 cc. Abreu (San Sebastian Hospital, Rio de Janeiro) describes a technique of pulmonary washing for the recovery of microorganisms. A needle is inserted between the cricoid and thyroid cartilages; 8 cc. of novotocaine (0.5 per cent) is then injected. After an interval of ten minutes 40 cc. of isotonic saline solution is slowly instilled, the table tilted and the patient kept in Trendelenburg

position for five minutes. Then the patient is turned into the knee-chest position for another five minutes, after which he is allowed to cough the contents into a hemorrhage box. Sixty to 80 cc. of material, largely broncho-alveolar secretions, will be returned. The only contraindication is recent hemoptysis. This method is without danger and is preferred by the patients to gastric lavage. It is simple, requires few instruments, and it is possible to recover tubercle bacilli and other organisms by this method which could not be obtained by any other.—*Lavado pulmonar en el diagnostico etio-patogenico o evolutivo de la tuberculosis*, M. de Abreu, *Prensa méd. argent.*, October 11, 1944, 31: 2025.—(W. Swienty)

BLOOD CELL COUNTS¹

Their Statistical Interpretation

WILLIAM N. BERG²

SYNOPSIS

I. Purpose

II. The Red Cell Count

- (1) Distribution of red cell counts: one source of variation, random streaming
- (2) Distribution of red cell counts: several sources of variation
- (3) Problem 1: What information is obtainable from a single red cell count?
- (4) Problem 2: What methods may be used in determining that a single chamber-count is correct?
 - Method 1: The count conforms to a criterion—a table of ranges
 - Method 2: Comparing the actual with the theoretical Poisson distribution
 - Method 3: Comparing the obtained 16-square counts with others in the literature
- (5) Problem 3: How large a difference between two consecutive red cell counts on the same blood may be due to random sampling?
 - Method 1: Comparing an obtained difference with others in the literature
 - Method 2: The difference conforms to a criterion—a table of ranges
 - Method 3: Calculating, from a formula, the probability that the difference could be produced by random sampling
 - Method 4: Can a population be found (table 2) from which both counts were probably drawn?
- (6) Problem 4: Are two red cell counts better than one?

III. The Total White Cell Count

- (1) Distribution of total white cell counts under conditions of careful routine
- (2) Problem 5: What information is obtainable from a single total white cell count?
- (3) Problem 6: What methods may be used in determining that a single chamber-count of total white cells is correct?
 - Method 1: The count conforms to a criterion—a table of ranges
 - Method 2: Comparing counts on single square millimeters with others in the literature
 - Method 3: Comparing the actual with the theoretical Poisson distribution
- (4) Problem 7: How large a difference between two consecutive total white cell counts may be due to random sampling?
 - Method 1: The difference conforms to a criterion—a table of ranges

¹ The Committee on Evaluation of Laboratory Procedures asked Mr. William N. Berg to prepare a report on the statistical evaluation of blood counts. The result is this paper. *The huge amount of work invested in this study will be obvious to any reader. But, since this work is entirely that of Mr. Berg, the Committee could not possibly appropriate it as its own report. However, the Committee is deeply grateful to Mr. Berg and wishes to recommend his paper to the careful attention of the readers of the Review.*

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Method 2: Comparing an obtained difference with others in the literature

Method 3: Calculating, from a formula, the probability that the difference could be produced by random sampling

Method 4: Can a population be found (table 7) from which both counts were probably drawn?

(5) Problem 8: Are two total white cell counts better than one?

IV. The Neutrophil Count

(1) Distribution of neutrophil counts

(2) Problem 9: What information is obtainable from a single neutrophil count?

(3) Problem 10: What methods may be used in determining that a single neutrophil count is correct?

Method 1: Make two counts in 2×100 white cells. Treat difference as in problem 11.

(4) Problem 11: How large a difference between two consecutive neutrophil counts on the same blood, on the same or on different smears, may be due to random sampling?

Method 1: Comparing an obtained difference with others in the literature

Method 2: The difference conforms to a criterion—a table of ranges

Method 3: Calculating, from a formula, the probability that the difference could be produced by random sampling

Method 4: Can a population be found (tables 11 and 12) from which both counts were probably drawn?

(5) Problem 12: Are two neutrophil counts better than one?

V. The Lymphocyte and Monocyte Counts

VI. Small Percentage Counts—Less than 5 per cent

I. PURPOSE

The main purpose of this paper is to describe the statistical aspects of blood cell counting so that the worker can make his own tests of significance by reading a table. First, the statistical distribution of a blood cell count and its implications are discussed. Then, problems that arise in blood cell counts are discussed with reference to the use of statistical concepts as aids in their solution.

Most of this paper is taken up with a series of comparisons between counts obtained in careful routine and research and the corresponding data obtained by mathematical-statistical methods.

Accuracy of figures: Due to rounding of fractions, to the nearest whole number, figures may be in error by one-half of one cell.

History: The stages in the development of the hemacytometer and counting methods are described by Plum (1).

All counts or differences between counts, so large that they can be produced by random streaming or sampling only 5 times in 1,000 trials, are regarded as incorrect or due to a change in the count. Charts 1 to 12 were drawn for this level of significance, $5/1000$. Other levels of significance be selected from the tabulated data.

II. THE RED CELL COUNT

(1) *Distribution of red cell counts: one source of variation, random streaming:* Let it be assumed that from a large single dilution of blood from hypothetical patient number 3,000,000, 1,000 correct red cell counts were made, each on 80 squares, using 1,000 identical counting chambers. Assume that the mean count is 300. The counts are shown in table 1, line 3. That the counts will be as indicated is shown by numerous investigations designed to test the agreement between statistical theory and actual count. Among these are the works of Plum (1) and Berkson, Magath and Hurn (2).

Line 3 may be read together with line 1 as follows: there were 21 counts (line 1) of 248 to 264 red cells; (line 3, columns 2 and 3): 136 counts of 265 to 282; 341 counts of 283 to 299 red cells, and so on. The mean of these 1,000 counts, 300 red cells, is shown on line 3, column 5. This may lead to a calculation of 3,000,000 red cells per mm.³ It should be noted that 300 is an actual count: 3,000,000 is not a count, but a calculation based on a count.

TABLE 1

Normal distributions of correct red blood cell counts obtainable from a single dilution pipet

LINE NUMBER	NUMBER OF COUNTS, OUT OF 1,000, THAT WILL FALL BETWEEN THE COUNTS BELOW							
1		21	136	341	341	136	21	
	Column number							
	1	2	3	4	5	6	7	8
	Patient number	Number of red blood cells on 80 squares each 1/400 mm. ²						
					Mean			
2	2,000,000	158	172	186	200	214	228	242
3	3,000,000	248	265	283	300	317	335	352
4	4,000,000	340	360	380	400	420	440	460
5	5,000,000	433	455	478	500	522	545	567
6	6,000,000	527	551	576	600	624	649	673
7	7,000,000	621	647	674	700	726	753	779

There are two extreme counts at the right and left ends of each line that have been omitted from table 1, but are included in the calculations.

Since the blood of patient number 3,000,000 was counted correctly 1,000 times, why should the counts vary from 248 to 352 red cells? They vary because there are "chance" or "purely accidental" variations in the way the red cells stream across the squares in the chamber.

The probabilities (line 1) of obtaining the various counts from the same dilution pipet may be considered in interpreting the count. Each line from 2 to 7 may be considered a base line to a normal curve; the curve is omitted since it is not needed here. All counts on each line cannot be shown for lack of space. Line 2, for example, starts at a count of 156, 157, 158, 159 up to 242, 243, 244. Each count is an abscissa.

On each line, the interval between two columns (standard deviation) is the square root of the mean count. Thus, for line 4 for the mean count of 400 red cells, the interval is the square root of 400, that is 20 red cells. Intermediate lines can be calculated easily from this relation between mean blood count and line interval (standard deviation). Barlow's Tables of Squares, Cubes, Square Roots (3) will be found very helpful.

Work of Plum (1): Plum's red cell counts may be chosen for study because their variation is due only to random streaming. In his Experiment 1, a standard dilution of ear-blood, diluted 1:200, containing 4.55 million red cells per mm.³ was used to fill the same chamber 17 times. "The red cell count is put down for every 16 small squares and 20 such groups are counted in each chamber." There were published 340 counts on 340 groups of 16 squares. There were, therefore, 68 counts on 80 squares, on the same blood in the same counting chamber. Mean of 68 counts was 461.0 red cells. The range was from 412 to 515 red cells. Plum found excellent agreement between statistical theory and actual counts. All 68 of the above counts should, and they do, fall on one line in table 1, between lines 4 and 5, for hypothetical patient number 4,610,000.

(2) *Distribution of red cell counts: several sources of variation:* According to Berkson, Magath and Hurn (2), table 1 may be used in interpreting a count made under some research conditions, but not as made in careful routine. In table 1, it is assumed that all chambers used measured exactly 1 mm. x 1 mm. x 0.1 mm. and the dilutions were all exactly 1 plus 199. According to Berkson (2) the line intervals (standard deviation) in table 1 should be corrected by adding the variations due to differences in size of chamber and pipet. In their work, involving several hundred counts, chambers and pipets differed in their sizes, but were within the tolerances prescribed by the National Bureau of Standards (4). The largest permissible chamber will hold 108 per cent of the contents of the smallest permissible chamber. The tolerances prescribed in 1925 and 1944 are the same. The Bureau is prepared to test a hemacytometer chamber and certify its depth and the dimensions of its central millimeter square. (Personal communication.)

Table 2 was calculated with the aid of Berkson's formula 5 (2). From formula 5, one can calculate the line interval (standard deviation) to include three sources of variation: (a) random streaming of cells over chamber squares, (b) variations in chamber size and (c) variations in dilution pipets. Whereas the line interval was 17 red cells for a count of 300 in table 1 (line 3), this is increased to 25 red cells for the same count in table 2 (line 12). Corresponding data in the two tables are not very different because the greater part of the variation in chamber-count is due to random streaming.

Reading table 2: Table 2 is read just as is table 1. For example, lines 1 and 12 are read together as follows: if it were possible to make a patient-count, that is, to count all the red cells in 1 mm.³ of blood while it is in the patient, and the number were 3,000,000, then, if 1,000 chamber-counts were made under conditions of careful routine with any chamber and pipet at hand, these counts would be distributed as shown on line 12. There would be 21 counts (line 1) of

TABLE 2

Normal distributions of correct red blood cell counts under conditions of careful routine
Based on Berkson's (2) Formula 5

LINE NUMBER	NUMBER OF COUNTS, OUT OF 1,000, THAT WILL FALL BETWEEN THE COUNTS BELOW							
		21	136	341	341	136	21	
1	Column number							
	1	2	3	4	5	6	7	8
	Patient number	Number of red blood cells on 80 squares each 1/400 mm. ²						
					Mean			
2	2,000,000	146	164	182	200	218	236	254
3	2,100,000	154	172	191	210	229	248	266
4	2,200,000	161	181	200	220	240	259	279
5	2,300,000	169	189	210	230	250	271	291
6	2,400,000	177	198	219	240	261	282	303
7	2,500,000	184	206	228	250	272	294	316
8	2,600,000	192	215	237	260	283	305	328
9	2,700,000	200	223	247	270	293	317	340
10	2,800,000	208	232	256	280	304	328	352
11	2,900,000	216	240	265	290	315	340	364 "
12	3,000,000	224	249	275	300	325	351	376
13	3,100,000	231	258	284	310	336	362	389
14	3,200,000	239	266	293	320	347	374	401
15	3,300,000	247	275	302	330	358	385	413
16	3,400,000	255	284	312	340	368	396	425
17	3,500,000	263	292	321	350	379	408	437
18	3,600,000	271	301	330	360	390	419	449
19	3,700,000	280	310	340	370	400	430	460
20	3,800,000	288	318	349	380	411	442	472
21	3,900,000	296	327	359	390	421	453	484
22	4,000,000	304	336	368	400	432	464	496
23	4,100,000	312	345	377	410	443	475	508
24	4,200,000	320	353	387	420	453	487	520
25	4,300,000	328	362	396	430	464	498	532
26	4,400,000	335	370	405	440	475	510	545
27	4,500,000	343	379	414	450	486	521	557
28	4,600,000	351	388	424	460	496	532	569
29	4,700,000	359	396	433	470	507	544	581
30	4,800,000	367	405	442	480	518	555	593
31	4,900,000	375	413	452	490	528	567	605

TABLE 2—*Concluded*

LINE NUMBER	NUMBER OF COUNTS, OUT OF 1,000, THAT WILL FALL BETWEEN THE COUNTS BELOW							
1		21	136	341	341	136	21	
	Column number							
	1	2	3	4	5	6	7	8
	Patient number	Number of red blood cells on 80 squares each 1/400 mm. ²						
32	5,000,000	383	422	461	500	539	578	617
33	5,100,000	391	431	470	510	550	589	629
34	5,200,000	399	439	480	520	560	601	641
35	5,300,000	407	448	489	530	571	612	653
36	5,400,000	415	457	498	540	582	623	665
37	5,500,000	423	465	508	550	592	635	677
38	5,600,000	431	474	517	560	603	646	689
39	5,700,000	439	483	526	570	614	657	701
40	5,800,000	447	491	536	580	624	669	713
41	5,900,000	455	500	545	590	635	680	725
42	6,000,000	463	509	554	600	646	691	737
43	6,100,000	471	518	564	610	656	702	749
44	6,200,000	479	526	573	620	667	714	761
45	6,300,000	487	535	582	630	678	725	773
46	6,400,000	496	544	592	640	688	736	784
47	6,500,000	504	553	601	650	699	748	796
48	6,600,000	512	561	611	660	709	759	808
49	6,700,000	520	570	620	670	720	770	820
50	6,800,000	528	579	629	680	731	781	832
51	6,900,000	536	588	639	690	741	792	844
52	7,000,000	545	596	648	700	752	804	855
53	7,250,000	564	618	671	725	779	832	886
54	7,500,000	584	639	695	750	805	861	916
55	7,750,000	603	660	718	775	832	890	947
56	8,000,000	622	682	741	800	859	918	978

224 to 248 red cells (line 12); 136 counts of 249 to 274; 341 counts of 275 to 299 and so on. The mean of these 1,000 counts is 300 (line 12, column 5) red cells counted on 80 squares.

Intermediate lines, if needed, may be calculated by adding or subtracting from the mean, the nearest line interval.

Each line from 2 to 56 may be considered a base line to a normal curve; the curve is omitted since it is not needed here. It is not practical to show all the counts belonging on a line. If this were done, line 12 would read: 222, 223, 224,

225 and so on up to 378. The outermost two counts are not shown in the table, although they are included in calculations.

(3) *Problem 1: What information is obtainable from a single red cell count?* Given a single chamber-count of 464 red cells on 80 squares, made under conditions of careful routine. What is the patient-count, that is, the count if it could be made while the blood is in the patient?

Referring to table 2, line 32, column 5, it may be noted that the blood of patient number 5,000,000, containing 5,000,000 red cells per mm.³, could be counted as 464 on 80 squares. For if 1,000 simultaneous chamber-counts were made on this patient, 341 counts (line 1) would fall between 461 and 500 red cells (columns 4 and 5). The blood of patient 4,000,000 will be counted 464 exactly (line 22, column 7). The blood of patient 6,000,000 will be counted as 464 exactly (line 42, column 2), but not so frequently.

TABLE 3

Different probabilities of obtaining the same chamber-count, 464 red cells on 80 squares, from different patients

PATIENT NUMBER	PROBABILITY OF OBTAINING A COUNT OF EXACTLY 464 RED CELLS ON 80 SQUARES	NUMBER OF COUNTS OUT OF 10,000 THAT WILL BE EXACTLY 464 RED CELLS ON 80 SQUARES
4,640,000	0.0108	108
5,000,000	0.0067	67
4,000,000	0.0017	17
6,000,000	0.0001	1
3,720,000	0.0001	1

Trying to decide which blood furnished the dilution that was counted is a problem in statistical mathematics known as "finding a universe (in this case, a large number of related patient-counts) from which the given sample (the chamber-count) may reasonably have been drawn." The sample may have been drawn from a number of universes, the probabilities of the drawing differ.

It may be noted in table 3 that the probability, 0.0108, of obtaining a count of 464 red cells from blood containing 4,640,000 red cells per mm.³ is greater than the probability of obtaining this same chamber-count on any other blood. But this does not in any way prevent the drawing of counts of 464 in other blood samples, in proportion to their respective probabilities.

Events having very small probabilities will happen. While there is only one chance in 10,000 ($P = 0.0001$) that a chamber-count of exactly 464 red cells on 80 squares will be obtained from patient number 6,000,000 (table 3), such an event, and others comparable to it, will happen. There are over 1,000,000 hospital beds in the United States. This implies several million blood counts annually. If there are 1,000,000 counts annually on patient number 3,720,000 in the United States, the blood of this patient is counted as 464 red cells on 80 squares, close to 100 times. This is the probability, 0.0001, multiplied by the number of counts, 1,000,000.

Chamber-counts greater than the mean plus twice the standard deviation (table 2, counts greater than column 7) and chamber-counts less than the mean minus twice the standard deviation (table 2, counts less than column 3) are in the literature. They represent counts associated with small probabilities. Of course, they must not be rejected offhand. Those who desire to work at a 95 per cent confidence limit may use table 2, ignoring 23 counts that are less than (to left of) column 3 and 23 counts greater than (to right of) column 7. Columns 3 and 7 include 954 counts out of 1,000, 954 being the sum of (line 1) 136, 341, 341, and 136. Working at the 95 per cent confidence limit means willingness to assume the risk of making errors of interpretation in 50 out of 1,000 correct counts.

Berkson (5) and associates made 10 chamber-counts on one specimen of blood. On 40 different specimens, 400 counts were made. Among these are the following 10 counts on one specimen of blood, using 10 different pipets into 10 different chambers: (their table 1, Exp. 9) 495, 464, 461, 513, 500, 450, 482, 572, 444, 523: mean, 490.4 red cells counted on 80 squares. Referring to table 2, line 31, column 7, it may be noted that one of the foregoing counts, 572, lies beyond the mean plus twice the standard deviation, 567 in this case. If 1,000 counts had been made on this specimen, there would have been only 23 counts out of the 1,000 exceeding 567. Five such small-probability counts were found in the above-mentioned publication. Generally, these small-probability counts cannot be found because there were too few counts on the same blood.

The answer to problem 1 is: a count of 464 red cells on 80 squares will be obtained on blood specimens containing anywhere from 3,720,000 (table 2, line 19, column 8) to 6,000,000 red cells per mm.³ (table 2, line 42, column 2). Another example: a count of 292 red cells was obtained. Any blood will be counted as 292, beginning with patient number 2,300,000 (table 2, line 5, column 8) to patient number 3,800,000 (table 2, line 20, column 2).

Chart 4 shows graphically the patient-count intervals obtainable from table 2.

(4) *Problem 2: What methods may be used in determining that a single chamber-count is correct?* According to Osgood (6, p. 473): "Count 5 groups of 16 small squares. These should not differ by more than 20 cells." According to War Department (7) *Methods for Laboratory Technicians* (p. 17): "The difference between the number of cells in any two blocks should not be more than 15 cells."

A series of papers on calculation of ranges of samples was begun by "Student" (12), continued by Pearson and associates (13, 14) and completed by Pearson and associates (18). Their works made it possible to calculate the range tables in this paper. These were calculated with the aid of Pearson's table 2 (18, p. 308).

Reading table 4: Ranges of samples of 5: Assume that many counts on 80 squares (5 x 16 squares) have been made on patient X, and the mean of all of these is 400 red cells. (All of these counts should fall on line 22 of table 2.) The differences in table 4, column headed 400, will apply to these counts, pro-

vided they are obtained under conditions of careful routine. For example, the difference (range) between largest and smallest count on 16 squares will exceed 29 red cells in 100 counts out of 1,000. In one count out of 1,000, the corresponding figure is 45 red cells.

When the only information available is a single count of 400, it must not be overlooked that a single count of 400 red cells may be obtained on all patients from patient number 3,200,000 (table 2, line 14, column 8) to patient number 5,200,000 (table 2, line 34, column 2) (or see chart 4). Hence, in reading table 4 for this single count of 400 red cells, one cannot tell exactly which column between 300 and 500 heading is to be read. To read conservatively, read the column headed with the smaller red cell count, 300 approximately in this case. A difference exceeding 33 red cells is improbable; if it exceeds 39, it points to error.

TABLE 4
Ranges of samples of 5

Out of 1,000 differences (ranges) between the largest and smallest counts of 5 groups of 16 squares, the number of differences shown below will exceed the indicated number of red cells. Differences between red cell counts are here assumed to be due only to random streaming. Based on Pearson (18) and Berkson's correction (2, p. 310).

NUMBER OF DIFFERENCES OUT OF 1,000	MEAN NUMBER OF RED CELLS COUNTED ON 80 SQUARES						
	100	200	300	400	500	600	700
	Difference between largest and smallest count on 16 squares red cells						
100	14	20	25	29	32	35	38
50	16	22	28	32	35	39	42
25	17	24	30	35	39	42	46
10	19	27	33	38	42	46	50
5	20	28	35	40	45	49	53
1	23	32	39	45	50	55	60

If the difference between the largest and smallest 16-square count exceeds table 4 differences at the 1 per cent level, the obtained difference exceeds 99 comparable differences. Since random streaming can produce this result, the conclusion that there is error is not obligatory. If the obtained difference exceeds table 4 differences at the 0.1 per cent level, chance will produce this result once in 1,000 similar counts. The investigator uses his own judgment in deciding whether the difference indicates error, or is the one-in-1,000 produced by random streaming.

Method 1: The count conforms to a criterion—a table of ranges. Step 1: Count red cells in 5 groups of 16 squares. Record the 5 counts separately. For the present purpose it is immaterial whether the 16 squares are at the 4 corners and centre of the field, or whether 4 rows of 20 squares are counted and recorded as 5 groups of 16.

Example: taken from Plum's (1) twelfth chamber-filling, 2" count: 114, 79, 119, 58, 122 red cells; total 492.

Step 2: Select the largest difference or range between any 2 groups. In the example: $122 \text{ minus } 58 = 64$.

Step 3: Compare the obtained difference with the differences in table 4. Select the column heading nearest to the actual total red cells counted.

In the example: when 500 red cells are counted, in one count out of 1,000, the difference or range will exceed 50 red cells. The above difference of 64 must be regarded as highly improbable.

DIFFERENCE BETWEEN
LARGEST AND SMALLEST COUNT
RED CELLS

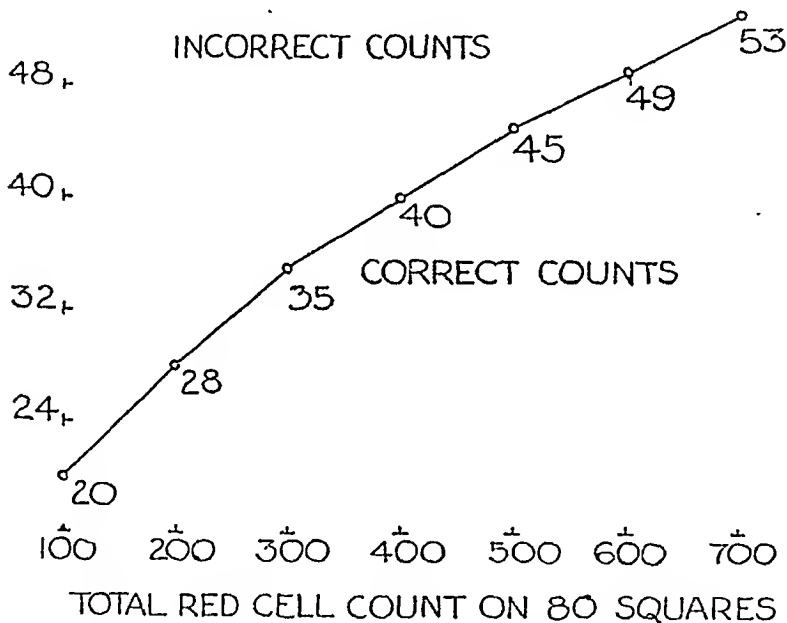


CHART 1. Red cell counts. To test correctness of a single count on 5 blocks of 16 squares.

Another example: Plum made 4 counts of 5×16 squares in each of 17 chamber-fillings with the same dilution. In the above, twelfth chamber-filling, the 3rd count was: 73, 106, 73, 93, 92; total 437 red cells. Difference: $106 \text{ minus } 73 = 33$. Referring to table 4, for counts of 400 red cells, a difference of 33 is to be expected in 50 such counts out of 1,000. The difference of 33 is, therefore, reasonable.

Chart 1 shows that any difference up to 40 would be acceptable, that is, it is within the 5/1000 level.

Sixty-eight differences calculated from Plum's (1) experiment 1 were compared with table 4, column headed 500 red cells. The mean of his 68 counts on 80 squares was 461 red cells. Omitting the largest difference of 64; there were eight differences exceeding 32 red cells, giving $8/67$ or 12 per cent (10 per cent, table 4); 5 differences exceeded 35 red cells, giving $5/67$ or 7.5 per cent (5 per

cent, table 4) and one difference exceeded 45 red cells, giving $1/67$ or 1.5 per cent (0.5 per cent, table 4).

Method 2: Comparing the actual, with the theoretical Poisson distribution. On account of the laborious calculations involved, it is not likely that this method will be used in routine. The method has been described by Berkson, Magath and Hurn (11, p. 417).

Method 3: Comparing the obtained 16-square counts with others in the literature. The only publication in which 16-square counts were found was that of Plum (1). The 340 counts ranged from 125 to 58 red cells on one group of 16 squares: mean, 92.2. Of course, comparisons are of value only when total counts are the same. Differences (ranges) between groups of 5×16 squares were: 46, 44, 39, 37, 36, 35, 34, 33, 32, 31 and 57 others, ranging from 30 down to 7 red cells. These counts were on the same dilution in the same chamber.

Assuming that problem 2 has been solved, and that the single count can be judged correct by objective standards, problem 1 still remains to be faced.

(5) *Problem 3: How large a difference between two consecutive red cell counts on the same blood may be due to random sampling?*

Method 1: Comparing an obtained difference with others in the literature. The differences between consecutive counts will be influenced by the conditions under which the chamber-counts are made. The differences summarized in table 5 were calculated as follows: count 1 minus count 2, count 2 minus count 3, etc., without altering the order of counts as found in a publication. Berkson (5) and Magath, Berkson and Hurn (9) published 130 counts on 13 blood specimens. Ten different pipets and 10 different chambers were used with one blood. In Plum's (1) Experiment 1, the same chamber was filled 17 times with the same dilution and 4 counts, each on 80 squares, were made on each filling. In Buerker's (10) 140 counts, 4 counts were made, on each of 35 fillings of an unstated number of chambers. In the investigation summarized in table 5 all counts were not far from 500 red cells; hence the differences are comparable.

Method 2: The difference conforms to a criterion—a table of ranges. Table 6 shows the minimum or unavoidable differences, calculated by statistical methods. The table may be used when two or more counts are made on the same chamber-filling. Under this condition, there is one source of variation in count; random streaming.

Reading table 6: Assume that 1,000 or more counts have been made on patient X and the mean count is 500 red cells on 80 squares. The column headed 500 will apply to the differences between two consecutive counts in the same chamber filling. For example: 10 differences (ranges) out of 1,000 will exceed 81 red cells; one difference will exceed 104. The differences in the counts of Plum (1) and Buerker (10) shown in table 5 may be tested by table 6, column headed 500. Plum's maximum of 75 is producible by random streaming. Buerker's difference of 100, which he obtained twice—counts were 581; 481 and 607; 507—would ordinarily lead one to doubt whether random streaming alone could produce such differences. Chart 2 shows the differences at

the 5/1000 level. When only one pair of counts is being considered, select that column heading nearest to the mean of both counts, or use method 3.

Table 6X was calculated to show the obtainable differences when there are several causes of variation in count, as in careful routine.

TABLE 5

Summary of differences between two consecutive red cell counts on the same blood, on 80 squares

INVESTIGATOR	NUMBER OF DIFFERENCES	DIFFERENCES		CAUSES OF DIFFERENCES
		Mean	Maximum	
		red cells		
Plum (1).....	51	25	75	random streaming
Buerker (10).....	105	30	100	random streaming
Berkson (2, 5).....	117	40	130	random streaming, differences between chambers and pipets

DIFFERENCE BETWEEN 2
TOTAL COUNTS

RED CELLS

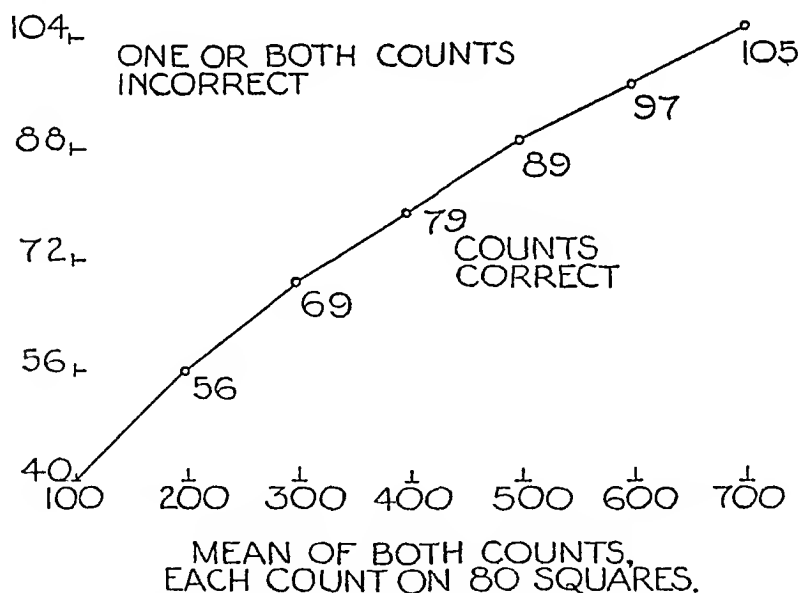


CHART 2. Red cell counts. To compare two counts in one filling of the counting chamber.

Berkson's maximum difference, 130 red cells, shown in table 5, may be tested by table 6X, column headed 500. The difference could be produced by random sampling in about 20 differences out of 1,000. Chart 3 shows the differences at the 5/1000 level.

Method 3: Calculating, from a formula, the probability that the difference

could be produced by random sampling. When only a single pair of chamber-counts, on the same or different blood specimens, is being considered, and it is desired to determine whether the difference between them could be produced by random streaming or by random sampling (includes several causes of variation), the following method, suggested by "Student" (William Sealy Gosset,

TABLE 6

Ranges of samples of two

Out of 1,000 differences (ranges) between two consecutive red cell chamber-counts, the number of differences shown below will exceed the indicated number of red cells. Variations in red cell counts are here assumed to be due only to random streaming. Based on Pearson (18).

NUMBER OF DIFFERENCES OUT OF 1,000	MEAN NUMBER OF RED CELLS COUNTED ON 80 SQUARES						
	100	200	300	400	500	600	700
	Difference between two consecutive counts red cells						
100	23	33	40	47	52	57	62
50	28	39	48	55	62	68	73
25	32	45	55	63	71	78	84
10	36	52	63	73	81	89	96
5	40	56	69	79	89	97	105
1	47	66	81	93	104	114	123

TABLE 6X

Ranges of samples of two

Careful routine conditions. Out of 1,000 differences between two consecutive red cell chamber-counts on the same blood, the number of differences shown below will exceed the indicated number of red cells. Based on Pearson (18) and Berkson's (2) Formula 5.

NUMBER OF DIFFERENCES OUT OF 1,000	MEAN NUMBER OF RED CELLS COUNTED ON 80 SQUARES						
	100	200	300	400	500	600	700
	Difference between two consecutive counts red cells						
100	26	43	59	75	90	105	121
50	31	51	70	89	107	126	144
25	36	59	80	102	123	144	165
10	41	67	92	117	141	165	189
5	45	74	101	127	154	180	207
1	53	86	118	149	180	211	242

1876-1937) (17, p. 355), may be used. The formula $\sqrt{(m_1 + m_2)/M}$ (where m_1 and m_2 are the mean red cell counts per square, the M the number of squares counted) is used to calculate the probability that the obtained difference could be produced by random sampling.

In table 2, the red cell counts on any line are separated by one or more line intervals or standard deviations. The symbol σ (sigma) is used to represent this

deviation. On line 2, for example, one sigma equals 18 red cells. Counts 200 and 254 are separated by 3σ . Counts 200 and 227 are separated by $27/18$ or 1.5σ . If the separation is greater than 3σ , the probability that both counts were correctly obtained on the same blood is so small as to justify the conclusion that one or both counts are in error. A probability table will not be needed if, as a rule, reject at 3σ , use data with caution at 2.5σ .

Three examples are discussed: (A) the counts are known to be on the same dilution, (B) the counts are known to be on different dilutions of the same puncture, and (C) there are 2 punctures, and the question is: has the blood

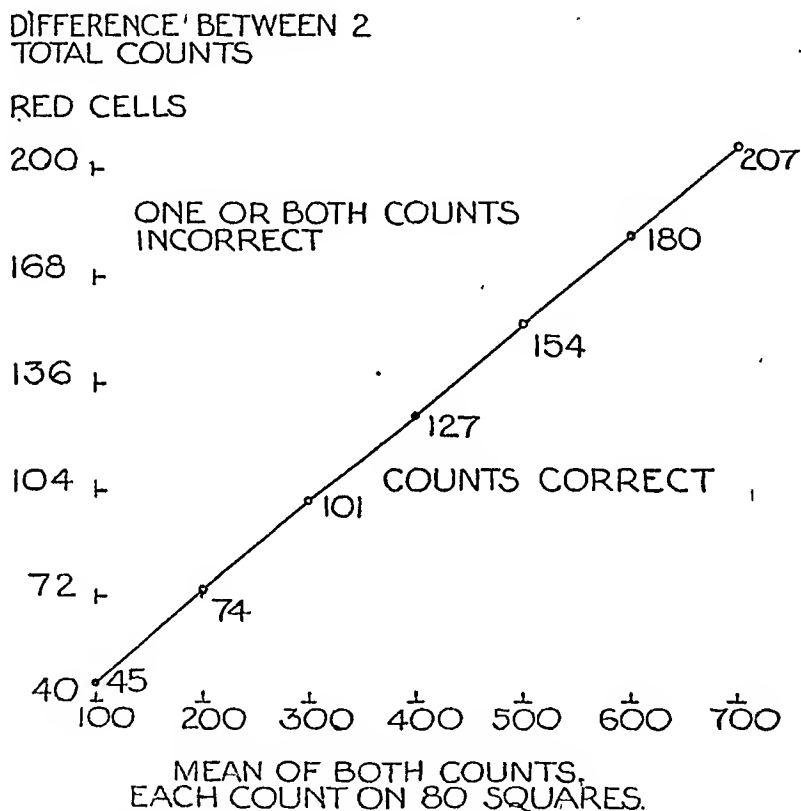


CHART 3. Red cell counts. To compare two counts from one puncture; but with different pipets and chambers.

count changed in the meantime? In the following method 3 it is assumed that both counts were made on the same number of squares, not necessarily 80.

(A) Example 1: Two counts from Plum's data (1) will be used. These are from the fifth chamber-filling, counts 3 and 4: 506 and 431 red cells.

Method for testing the significance of the difference between two red cell counts. Step 1: Subtract one count from the other: In example 1, it is plus or minus 75 red cells.

Step 2: Find the square root of the sum of the counts. In example 1: $506 + 431 = 937$, $\sqrt{937} = \pm 30.61$ red cells. This is the needed standard deviation of differences.

Step 3: Divide the difference by its standard deviation: In example 1: $75/\pm 30.61 = \pm 2.45\sigma$

Step 4: Interpret the quotient, 2.45 sigma, by reading its probability in the normal probability table. For 2.45 sigma the probability found is 0.014. This means that if Plum had obtained 1,000 differences on this same dilution without error, 14 differences would have been 75 or more. Seven of these would be minus 75 or more; 7 other differences would have been plus 75 or more.

Following the above stated rule: reject at 3 sigma, use data with caution at 2.5 sigma, the difference may be produced by random streaming, but not very often—14 times in 1,000.

(B) Example 2: The counts are known to be on different dilutions of the same puncture.

From the data of Magath, Berkson and Hurn (9, Experiment 2): 10 dilutions from one puncture were counted. Among these are 378 and 469 red cells on 80 squares. Could this difference have been produced by random sampling? Method 3, step 2 must be modified. The needed standard deviation or line interval must now include the "scatter" of count, not alone for random streaming (as in example 1) but also for differences in pipets and chambers.

Step 1: Subtract one count from the other. In example 2 this is plus or minus 91.

Step 2: Calculate the needed standard deviation (line interval) from the formula: σ_d (for differences) = $\sqrt{\sigma_1^2 + \sigma_2^2}$, where σ_1 and σ_2 are line intervals in table 2. For count 378, locate 380 in column 5, line 20. The interval or standard deviation is 31 red cells. For count 469, locate 470 in column 5, line 29, the interval is 37. $\sqrt{31^2 + 37^2} = 48.27$ red cells: the standard deviation required.

Step 3: Divide the difference by its standard deviation: $91/48.27 = 1.88\sigma$.

Step 4: Following the rule suggested above, 1.88σ is well within the 2.5σ limit which includes 988 out of 1,000 counts or differences. The difference of 91 red cells could be produced by random sampling. To see whether this is an agreement with table 6X: the normal probability table indicates that 94 per cent of counts or differences are included between -1.88σ and $+1.88\sigma$. Therefore, 6 per cent or 60 differences out of 1,000 will exceed 91 red cells. This compares with about 46 out of 1,000 in table 6X, column headed 400.

(C) Example 3: There are two punctures; the question is: has the patient-count changed in the meantime?

Buerker (10) counted his own blood: April 2, 1911, count was 459; April 6; count was 607 red cells on 80 squares. Following through the steps in example 2, one obtains $148/58.41 = 2.53\sigma$. Random sampling could produce the difference. If the difference had risen to 3σ , that is, 3×58.41 or 175 red cells, it would be reasonable to suppose that the patient-count had changed.

Method 4: Can a population be found (table 2) from which both counts were probably drawn? If two counts can be found on any line in table 2, they are obtainable on the same dilution. The difference between them is due to random sampling; that is, random streaming plus differences between pipets and cham-

bers. Usually two correct counts can be found on several lines close to each other. In the absence of other information one line is as good as another. Conversely, when two counts known to have been obtained on one blood specimen, cannot be found on one line in table 2, or are on one line but are separated by three or more line intervals, the difference between counts is due to error as well as random sampling. Chart 4 may also be used.

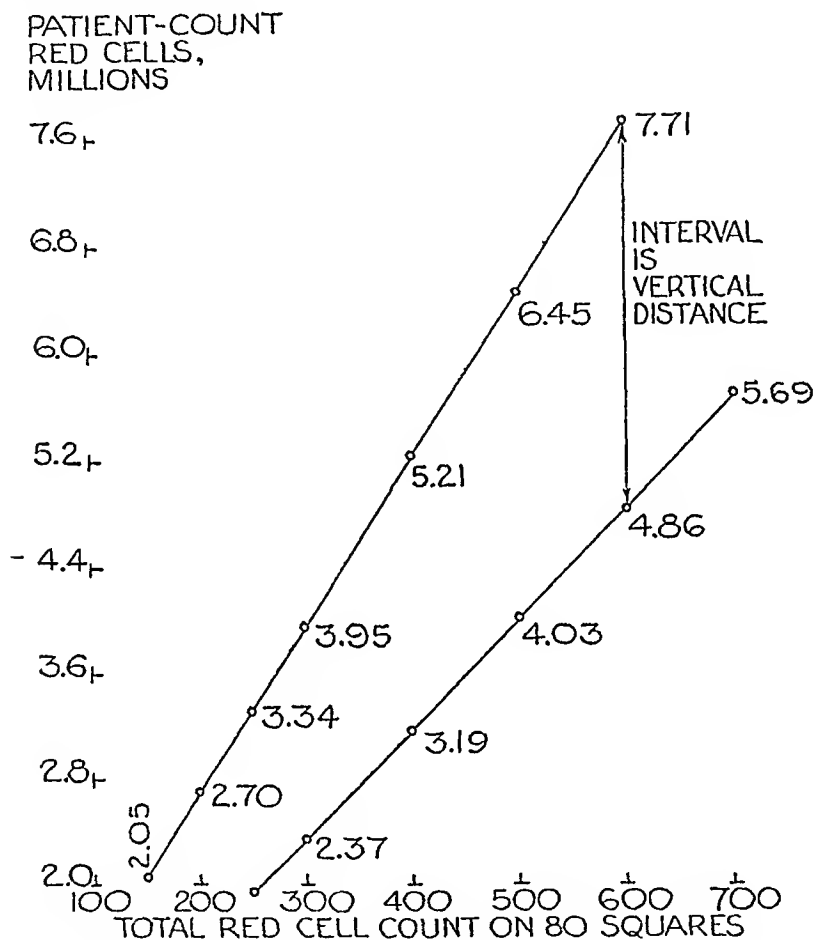


CHART 4. Red cell counts. To obtain the patient-count interval from a single chamber count.

When two counts have been obtained from the same chamber-filling their difference is presumably due to random streaming only. If two such counts can be found on one line in table 1, they are obtainable on the same dilution. If not, error is part of the difference.

When a pair of counts are tested by more than one method, the conclusions should be the same.

"A comparison of the two methods of treatment illustrates the general principle, so often lost sight of, that tests of significance, in so far as they are accurately carried out, are bound to agree, whatever process of statistical reduction may be employed." (Fisher (25), p. 198.)

(6) *Problem 4: Are two red cell counts better than one?* The mean of two counts may be a poorer estimate of the patient-count than the first count. Following data from Plum (1), fifth chamber-filling, counts 2 and 3, are illustrative. Investigator X made two consecutive counts of 471 and 506 red cells on 80 squares, in the same chamber-filling. He reported the mean 488 and, therefore, a patient-count of 4,880,000 red cells per mm.³ Unknown to investigator X, 66 other counts had been made on this same dilution; mean of 68 counts, 461; patient-count 4,610,000. If investigator X had reported 4,750,000 based on his first count, the error would have been 140,000. The actual report, 4,880,000, was in error by 270,000.

About one-third of the consecutive chamber-counts studied gave means that were poorer estimates of the patient-count than the first count. If the first chamber-count happens to be close to the patient-count, chance will place the second count further away, making their mean a poorer estimate than the first count, as in the example above. Conversely, if the first count is far from the patient-count, chance will place the second count nearer, and the mean of these two will be a better estimate than the first count. Since the investigator cannot tell which situation he is facing, the mean of two counts cannot be depended upon to furnish a better estimate of the patient-count than either one alone. For practically all other purposes, two counts are better than one.

III. THE TOTAL WHITE CELL COUNT

(1) *Distribution of total white cell counts under conditions of careful routine:* Let it be assumed that from one large dilution of blood from hypothetical patient number 3,500, 1,000 correct total white cell counts were made, each on 4 squares, each square 1 mm.² in area. Large numbers of chambers and pipets were used, take at random. Assume that the mean of the 1,000 counts was 70 white cells.

The counts will be distributed as shown in table 7, line 2. This may be read together with line 1: there were 21 counts (line 1) ranging from 41 to 50 white cells (line 2, columns 2 and 3); there were 136 counts (line 1) ranging from 51 to 59 white cells (line 2, columns 3 and 4) and so on. At least three causes contribute to the variations in these counts: (1) random streaming of white cells across the squares; (2) variations in sizes of chambers; (3) variations in pipets. In a statistical study of these factors, Berkson, Magath and Hurn (2, p. 318) derived a formula for easily calculating the extent to which these factors may influence the chamber-count.

On each line the interval between two columns (standard deviation) was calculated with the aid of Berkson's (2) formula 7. Thus, when the mean count is 100 white cells (line 5, column 5) the line interval (standard deviation) is 12 white cells. Theoretically, if identical technique were used, leaving random streaming as the only cause of variation in count, the line interval would equal the square root of the mean count. For line 5, the line interval would be the square root of 100 or 10. The difference between 10 and 12 white cells represents the variation due to laboratory technique; it is not error.

TABLE 7

Normal distributions of correct total white cell counts under conditions of careful routine
Based on Berkson's (2) Formula 7

LINE NUMBER	NUMBER OF COUNTS, OUT OF 1,000, THAT WILL FALL BETWEEN THE COUNTS BELOW							
1		21	136	341	341	136	21	
	Column number							
	1	2	3	4	5	6	7	8
	Patient number	Number of white cells on 4 squares, each 1 square millimeter						
					Mean			
2	3,500	41	51	60	70	80	89	99
3	4,000	49	59	70	80	90	101	111
4	4,500	56	68	79	90	101	113	124
5	5,000	64	76	88	100	112	124	136
6	5,500	72	84	97	110	123	136	148
7	6,000	79	93	106	120	134	147	161
8	6,500	87	101	116	130	144	159	173
9	7,000	95	110	125	140	155	170	185
10	7,500	102	118	134	150	166	182	198
11	8,000	110	126	143	160	177	194	210
12	8,500	117	135	152	170	188	205	223
13	9,000	125	144	162	180	198	216	235
14	9,500	134	152	171	190	209	228	246
15	10,000	142	161	181	200	219	239	258
16	10,500	149	169	190	210	230	251	271
17	11,000	157	178	199	220	241	262	283
18	11,500	164	186	208	230	252	274	296
19	12,000	172	195	217	240	263	285	308
20	12,500	180	203	227	250	273	296	320
21	13,000	188	212	236	260	284	308	332
22	13,500	196	221	245	270	295	319	344
23	14,000	204	230	255	280	305	330	356
24	14,500	213	238	264	290	316	342	367
25	15,000	221	247	274	300	326	353	379
26	15,500	228	255	283	310	337	365	392
27	16,000	236	264	292	320	348	376	404
28	16,500	244	273	301	330	359	387	416
29	17,000	252	282	311	340	369	398	428
30	17,500	260	290	320	350	380	410	440
31	18,000	268	299	329	360	391	421	452

TABLE 7—*Concluded*

LINE NUMBER	NUMBER OF COUNTS, OUT OF 1,000, THAT WILL FALL BETWEEN THE COUNTS BELOW							
		21	136	341	341	136	21	
	Column number							
	1	2	3	4	5	6	7	8
	Patient number	Number of white cells on 4 squares, each 1 square millimeter						
32	18,500	276	307	339	370	401	433	464
33	19,000	284	316	348	380	412	444	476
34	19,500	292	324	357	390	423	456	488
35	20,000	300	334	367	400	433	466	500
36	22,500	341	377	414	450	486	523	559
37	25,000	381	420	460	500	540	579	619
38	27,500	421	464	507	550	593	636	679
39	30,000	461	507	554	600	646	693	739

If all the counts on patient number 5,000 were shown, line 5 would read' 62, 63, 64, 65 . . . up to 135, 136, 137, 138.

(2) *Problem 5: What information is obtainable from a single total white cell count?* Given a single chamber-count of a total of 95 white cells, counted on 4 squares, each 1 mm.², chamber depth 0.1 mm., what is the patient-count, that is the count if it could be made while the blood is in the patient?

Referring to table 7, line 9, column 2, it may be noted that a chamber-count of 95 could be obtained on patient number 7,000. Out of 1,000 counts correctly made on a single dilution (1 plus 19) or on several punctures of patient number 7,000, two counts will be 94 or less; (line 1) 21 counts will range from 95 to 109; 341 counts will range from 125 to 139 (lines 1 and 9, columns 4 and 5).

Referring to line 2, columns 7 and 8; a chamber-count of 95 white cells could be obtained on patient number 3,500, because out of 1,000 chamber-counts on this patient 21 (line 1) will fall between 89 and 98. A single chamber-count of 95 white cells is obtainable, therefore, on all specimens of blood from patient number 7,000 to patient number 3,250. (See chart 8.)

Table 8 (similar to table 3) indicates how often the blood of various patients will be counted as exactly 95 total white cells. In the absence of other counts, for a single chamber-count of 95, the most probable patient-count is 4,750. But out of 10,000 chamber-counts on patient number 4,750, only 343 will be exactly 95. The gap is larger when the chamber-count is larger. For example; a chamber-count of 200 total white cells is obtainable on all patients from patient number 7,600 to patient number 13,750.

(3) *Problem 6: What methods may be used in determining that a single chamber-count of total white cells is correct?*

Method 1: The count conforms to a criterion — a table of ranges. An obtained difference (range) between the largest and smallest counts on 4 squares, each 1 mm.², is compared with differences calculated on a statistical basis, as in table 9.

Reading table 9: Assume that 1,000 or more white cell counts have been made on patient X. Each count was made on 4 squares, each 1 mm.², chamber-depth 0.1 mm., dilution 1 plus 19. Assume that the mean of the counts is 200. The

TABLE 8

Different probabilities of obtaining the same chamber-count, 95 total white cells on 4 squares, each 1 mm.², from different patients

PATIENT NUMBER	PROBABILITY OF OBTAINING A COUNT OF EXACTLY 95 WHITE CELLS ON 4 SQUARES	NUMBER OF COUNTS OUT OF 10,000, THAT WILL BE EXACTLY 95
4,750	0.0343	343
6,000	0.0054	54
7,000	0.0003	3
3,250	0.0001	1

TABLE 9

Ranges of samples of four

Out of 1,000 differences between the largest and smallest counts on 4 squares, each 1 mm.², the number of differences shown below will exceed the indicated number of white cells. Differences between white cell counts are here assumed to be due only to random streaming. Based on Pearson (18).

NUMBER OF DIFFERENCES OUT OF 1,000	MEAN NUMBER OF WHITE CELLS COUNTED ON 4 SQUARES EACH 1 SQUARE MILLIMETER				
	50	100	200	300	400
	Difference between largest and smallest count on 1 square millimeter white cells				
100	11	16	23	28	32
50	13	18	26	31	36
25	14	20	28	34	40
10	16	22	31	38	44
5	17	23	33	41	47
1	19	27	38	46	53

column headed 200, table 9, applies to these counts. In 100 out of 1,000 counts, the difference between the largest and smallest counts will exceed 23 white cells. In 5 out of 1,000, the difference will exceed 33.

When only a single count is available, 200 for example, it must not be overlooked that this count may be obtained on all patients from patient number 7600 (table 7, column 8, between lines 10 and 11) to patient number 13,750 (table 7, column 2, between lines 22 and 23).

In reading table 9 one cannot tell exactly which column between 152 and 275 is to be read. Close reading is usually not needed. For a single count of 200,

the most probable patient-count is 10,000, and the column headed 200 may be used. More conservatively, the column headed 150 (by mental interpolation between 100 and 200) might be read. Assume that, with a single count of 200, the range was 28. Reading column headed 150, in 5 counts out of 1,000, the difference between the largest and smallest count will exceed 28. (See chart 5.)

It is desirable to compare the theoretical differences of table 9 with those obtainable from the literature.

Method 2: Comparing obtained counts on single square millimeters with others in the literature. Separate records of counts on single square millimeters were found in only one publication, that of Bryan and Garrey (15). From one

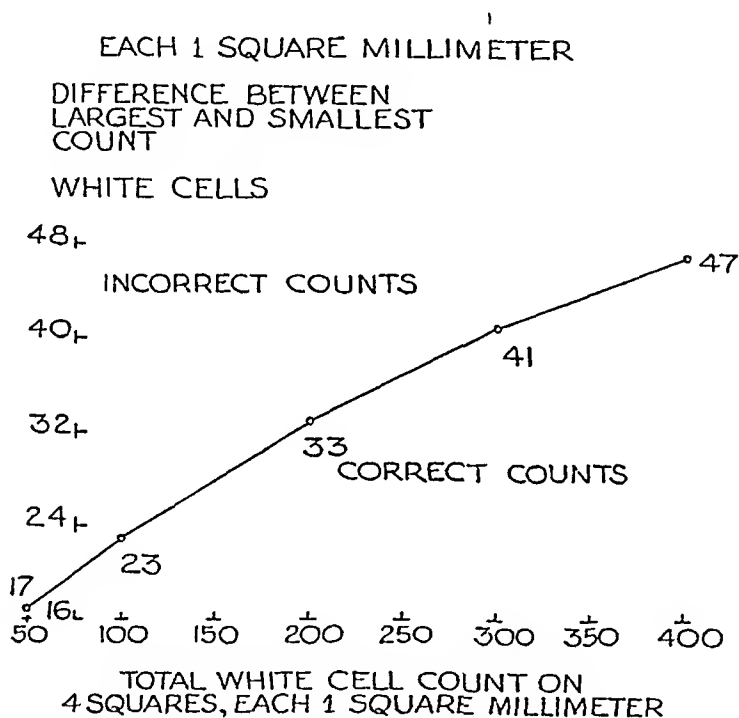


CHART 5. White cell counts. To test correctness of a single count on 4 squares.

blood, 2 pipets were filled. One pipet was shaken in one plane (their table 1), the other was shaken in a "rotor" (their table 2). From each pipet, 19 chamber-fillings were obtained, giving a total of 19×9 or 171 counts of white cells on single squares of 1 mm^2 . There were 342 counts in both tables.

When the pipet was shaken in one plane only, the differences between largest and smallest counts on 4 squares were: 68, 34, 30, 29 and 33 other lesser differences (ranges). Total white cells on 4 squares were: minimum, 126, mean, 174, maximum 271. According to table 9, bottom line, for a mean of 174 white cells, one count out of 1,000 will have a range exceeding 35. The above difference of 68 is due partly to random streaming and partly to error. The other differences of 34, 30, etc. seem reasonable. Results after shaking the pipet in the "rotor" were: total white cells on 4 squares, minimum 146, mean 166,

maximum 185. Differences between largest and smallest counts on 4 squares were: 19, 17, 16, 16 and 33 other lesser differences.

Method 3: Comparing the actual with the theoretical Poisson distribution. On account of the laborious calculations involved, it is not likely that this method will find use in routine. The method has been described by Yates and Batt (16).

Assuming the problem 6 has been solved, and the single count can be judged correct, problem 5 still is to be faced, namely, how to obtain the patient-count from one or more chamber-counts.

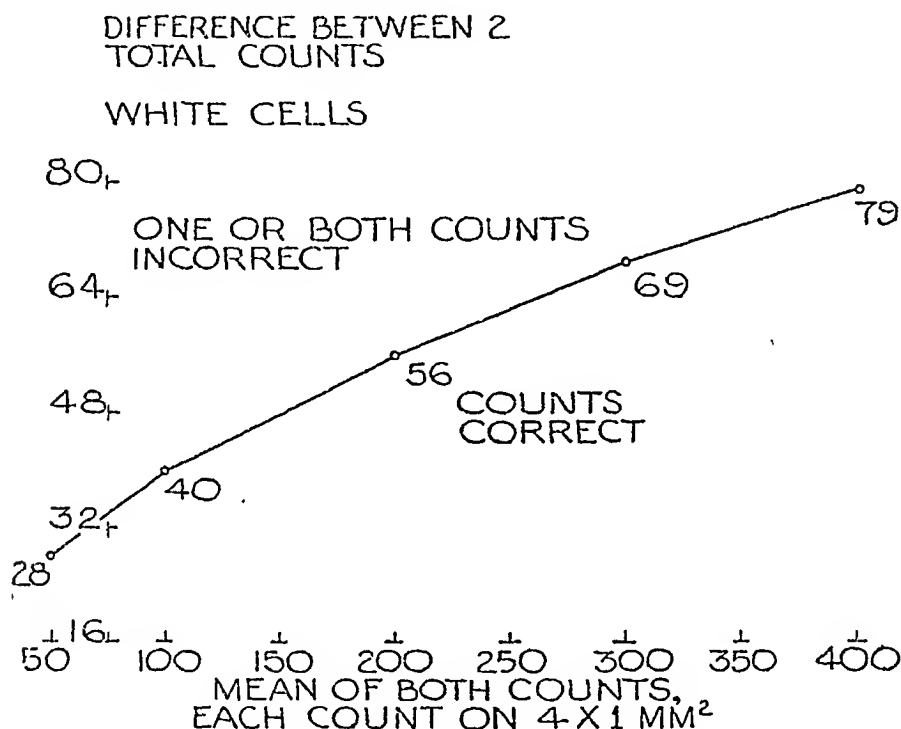


CHART 6. White cell counts. To compare two counts in one filling of the counting chamber.

(4) *Problem 7: How large a difference between two consecutive total white cell counts may be due to random sampling?*

Method 1: The difference conforms to a criterion—a table of ranges. Reading table 10: This shows the differences, as calculated by statistical methods, when these are due to random streaming only. A single difference in table 10 is obtained as follows: count 8 squares (each 1 mm.²), making two counts on 4 squares. The difference between the two counts makes one difference. Assume that 1,000 or more such differences were obtained on patient X, and the mean count was 200 white cells on 4 squares. The column headed 200 can be applied to the differences. Out of 1,000 differences, 100 will exceed 33; one difference will exceed 66 white cells. Data for the 5/1000 level are shown in chart 6.

Reading table 10X: This is read just like table 10. Under conditions of

careful routine, the differences in table 10 do not hold. For routine conditions, table 10X was calculated by combining the theoretical data of Pearson (18) with the appropriate standard deviation obtained in actual counts, by Berkson, Magath and Hurn (2). Data for the 5/1000 level are shown in chart 7. Com-

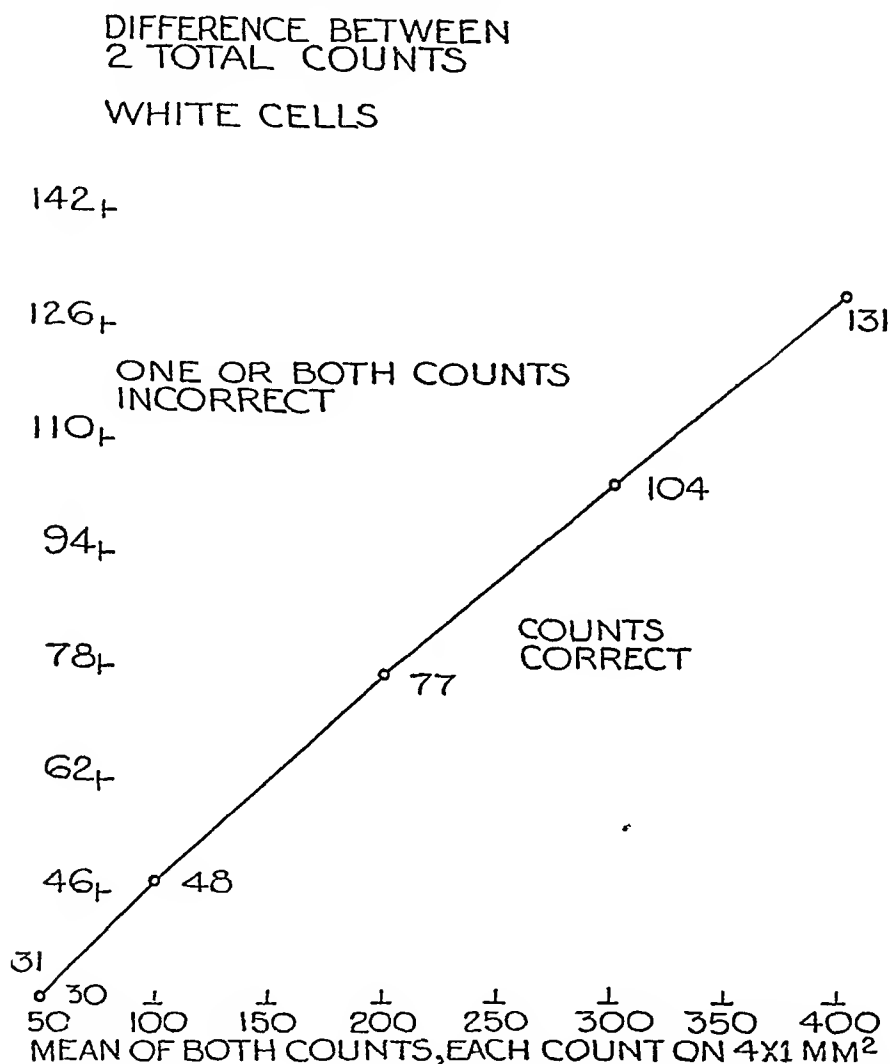


CHART 7. White cell counts. To compare two counts from one puncture but with different pipets and chambers.

parisons between actual differences in the literature and tables 10 and 10X follow.

Method 2: Comparing an obtained difference with others in the literature. From the tables of Bryan and Garrey (15), 37 differences were calculated from their table 1 by taking count 1 minus count 2, count 2 minus count 3, etc., without changing the order in which these are found (see method 1 above). Mean count: $17\frac{1}{2}$ white cells on 4 squares. Differences between consecutive

counts were 73, 59, 46, 45 and 33 lesser differences. Reading table 10: one difference out of 1,000 will exceed 66 white cells when the mean count is 200. Part of the above difference of 73 probably is error. The other differences, beginning with 46, are accounted for by random streaming.

TABLE 10

Ranges of samples of two

Out of 1,000 differences between two consecutive total white cell counts, the number of differences shown below will exceed the indicated number of white cells. Differences between total white cell counts are here assumed to be due only to random streaming. Based on Pearson (18).

NUMBER OF DIFFERENCES OUT OF 1,000	MEAN NUMBER OF WHITE CELLS COUNTED ON 4 SQUARES EACH 1 SQUARE MILLIMETER				
	50	100	200	300	400
	Difference between two consecutive counts white cells				
100	16	23	33	40	47
50	20	28	39	48	55
25	22	32	45	55	63
10	26	36	52	63	73
5	28	40	56	69	79
1	33	46	66	81	93

TABLE 10X

Ranges of samples of two

Out of 1,000 differences between two consecutive total white cell counts, the number of differences shown below will exceed the indicated number of white cells. Conditions: careful routine. Based on Pearson (18) and Berkson's (2) Formula 7.

NUMBER OF DIFFERENCES OUT OF 1,000	MEAN NUMBER OF WHITE CELLS COUNTED ON 4 SQUARES EACH 1 SQUARE MILLIMETER				
	50	100	200	300	400
	Difference between two consecutive counts white cells				
100	18	28	45	61	77
50	22	33	54	73	92
25	25	38	61	83	105
10	28	44	70	96	120
5	31	48	77	104	131
1	36	56	90	122	154

The above difference, 73, is between two counts, 198 and 271 white cells, counted in one chamber-filling. If these counts had been obtained on the same dilution, but with different pipets and chambers, table 10 would not apply. Reading table 10X, column headed 200, a difference of 73 is not far from the 5 out of 1,000 level, often regarded as indicating error.

A comparison with table 10X can be made with 17 differences calculated from 18 counts on the same dilution, made by Yates and Batt (16). Different

pipets and chambers were used. Differences are: 55, 38, 37, 35, 34 and 12 smaller differences. Mean of 18 counts on 4 squares: 142 total white cells. Random sampling can account for all the differences.

In another series, from one puncture 2 pipets were filled, two counts were made in different chambers, on 4 squares. Ten differences, from 10 patients, were 45, 45, 43 and 7 smaller differences. For one of these patients the counts were 173, and 128, with difference, 45. Referring to column 150 in table 10X, difference of 45 or more will occur in 50 differences out of 1,000.

The counts by Yates and Batt (16) having been made on 5 or 10 squares, each 1 mm.², were calculated to 4 squares, for the above data.

Method 3: Calculating, from a formula, the probability that the difference could be produced by random sampling. Example 1: This method, suggested by Student (17) has been discussed in detail in problem 3, method 3. As an example, two counts in the same filling of the chamber by Bryan and Garrey (15) were 198 and 271 white cells, each count on 4 squares. Could random streaming produce this difference of 73 white cells? Following through the steps outlined in problem 3, method 3, example 1: the answer for the above difference is 3.37σ . This being beyond the limit of 3σ suggested in problem 3 as a reasonable limit beyond which error may be suspected, it may be concluded that one or both counts are not correct for the single dilution counted.

Example 2: When two counts are known to be on different dilutions of the same puncture, the steps in problem 3, method 3, example 2, may be followed. Table 7 is here used.

Example 3: The counts from two punctures, different dates. Has the patient-count changed in the meantime?

From Medlar (23) following counts were obtained: Case Lo: 5/15, 256 total white cells, on 4 squares; on 5/19, 158 white cells. Is the difference, 98, due to a change in the patient-count? Following through the steps in problem 3, method 3, example 2 or 3, the answer is 3.38σ . The difference is too great to be accounted for by random sampling; a change in the patient-count is indicated. Table 7, column 5, is used to obtain standard deviation (line intervals) of the counts.

Method 4: Can a population be found from which both counts were probably drawn? If two counts can be found on one line in table 7 (or in one vertical interval, chart 8), both counts are obtainable on the same dilution under conditions of careful routine. If the counts are separated by more than 3 line intervals, the probability that both were correctly obtained on the same dilution is so small as to justify the conclusion (1) one or both are incorrect, or (2) both counts were correctly obtained on different dilutions.

The above counts (example 3) 158 and 256 can be found in table 7, lines 15, 16, 17, separated by 4 line intervals, indicating a change in white cell count.

(5) *Problem 8: Are two total white cell counts better than one?* As shown in problem 4, the mean of two counts may be a poorer estimate of the patient-count than the first count taken alone. As an example, the two consecutive

total white cell counts, 198 and 271, each counted on 4 squares, may be used. These were obtained on the sixteenth chamber-filling, in Bryan and Garrey's (15) table 1.

The mean count was 174. If an investigator had reported the first count in the usual manner, the chamber-count would be recorded as a patient-count of 9,900 white cells, in 1 mm.³ of blood. The error is 1,200 white cells. If the

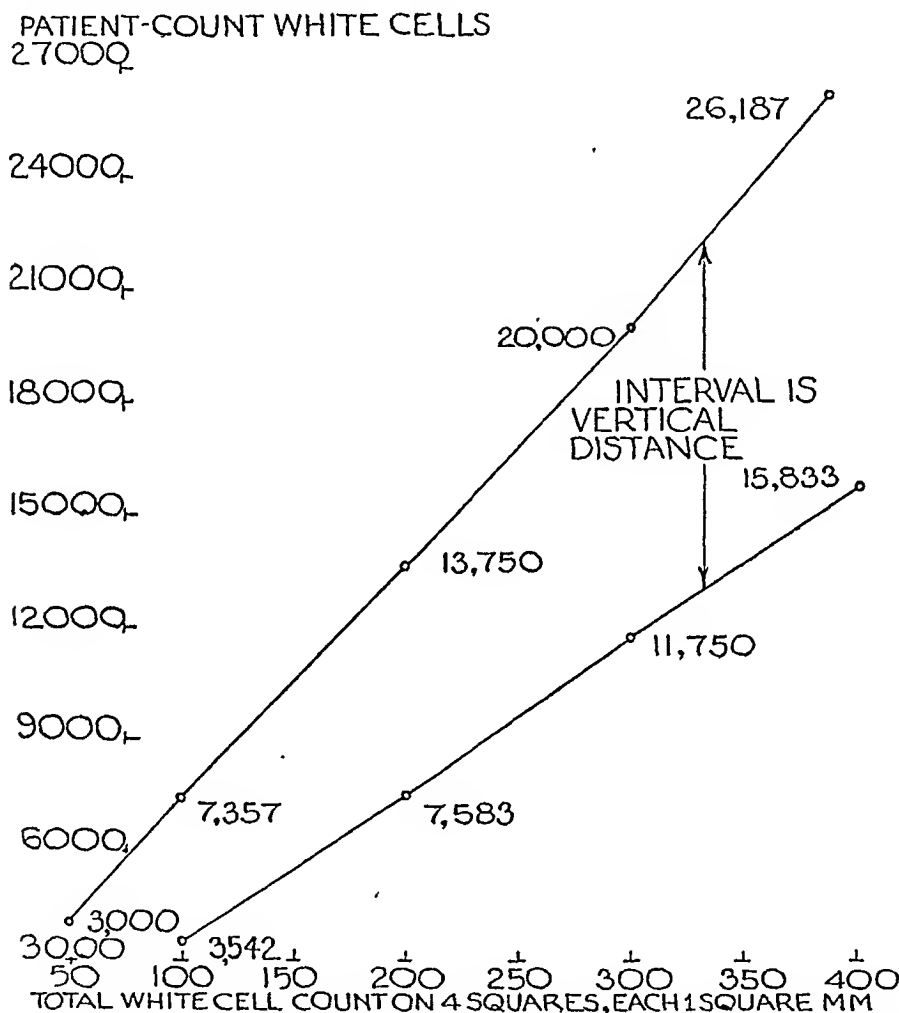


CHART 8. White cell counts. To obtain the patient-count interval from a single chamber count.

mean of the above counts, 235, were used, the patient-count recorded would be 11,750 and the error, 1,850 white cells, is one and one half times the first error.

IV. THE NEUTROPHIL COUNT

(1) *Distribution of neutrophil counts.*

"It was suggested to us that so many were the errors in making a count that the statistical error was of very little importance. Our view, however, was that these other errors

which are truly experimental could be kept sufficiently constant if a standard technique was adopted so that the only error with which one need be concerned was the statistical one. This is true, of course, when the question of comparison of counts is being considered. To demonstrate this point, one of us made a large number of smears from a single sample of blood. Twenty regular smears were selected and 200 cells counted from each smear. In every case similar parts of the smear were chosen for counting. The results are given in table 2." (Goldner and Mann (19).)

Mainland, Coady and Joseph (20) published a set of 21 differential counts on 7 drops of blood from the same person, Student, number 24. They made three counts of 100 on each of 7 slides. These investigators show that, with

TABLE 11

Distributions of correct neutrophil counts under conditions of careful routine, when total white cell count is 100

LINE NUMBER	NUMBER OF COUNTS OUT OF 1,000 THAT WILL FALL BETWEEN THE COUNTS BELOW							
		21	136	341	341	136	21	
	Column number							
	1	2	3	4	5	6	7	8
	Patient number	Number of neutrophils counted when total count is 100 white cells						
					Mean			
2	100.10	1	4	7	10	13	16	19
3	100.20	8	12	16	20	24	28	32
4	100.30	16	21	25	30	35	39	44
5	100.40	25	30	35	40	45	50	55
6	100.50	35	40	45	50	55	60	65
7	100.60	45	50	55	60	65	70	75
8	100.70	56	61	65	70	75	79	84
9	100.80	68	72	76	80	84	88	92
10	100.90	81	84	87	90	93	96	99

care, experimental error can be reduced to a negligible quantity. A comprehensive and very informative statistical study of the distribution of white cells in smears was made by Gyllenswärd (21). A recent review was published by Sturgis and Bethel (22).

Reading table 11: Assume that 1,000 differential counts, each of 100 total white cells, were made on patient X, and the mean number of neutrophils was 70. Locate 70 in the table, column 5, lines 1 and 8 are read together: 21 counts (line 1) will fall between 56 and 60 neutrophils (line 8, columns 2 and 3); 136 counts will fall between 61 and 64 neutrophils and so on. Table 11 may be used for any other differential cell count, lymphocytes, eosinophils, etc., provided the type of cell counted be 10 or more per cent of the total. The line interval (standard deviation) was calculated from the formula: square root of the product: total count times per cent neutrophils times per cent non-neutrophils. For line 8, the interval is 4.58 neutrophils.

Reading table 12: This is similar to table 11, except that table 12 is for the total count of 200 white cells. Goldner and Mann's (19) tables are for counts of 200 and 500 at 95 per cent confidence limit. Table 12 may be used for any other type of differential cell count, provided the type of cell counted is 5 or more per cent of the total count.

When the cell type is less than 5 per cent of the total count, table 15, (Berg (26)) may be used. (See section VI.)

TABLE 12

Distributions of correct neutrophil counts under conditions of careful routine, when total white cell count is 200

LINE NUMBER	NUMBER OF COUNTS OUT OF 1,000 THAT WILL FALL BETWEEN THE COUNTS BELOW							
1		21	136	341	341	136	21	
	Column number							
	1	2	3	4	5	6	7	8
	Patient number	Number of neutrophils counted when total count is 200 white cells						
					Mean			
2	200.10	1	4	7	10	13	16	19
3	200.20	7	12	16	20	24	28	33
4	200.30	15	20	25	30	35	40	45
5	200.40	23	29	34	40	46	51	57
6	200.50	32	38	44	50	56	62	68
7	200.60	41	47	54	60	66	73	79
8	200.70	50	57	63	70	77	83	90
9	200.80	59	66	73	80	87	94	101
10	200.90	69	76	83	90	97	104	111
11	200.100	79	86	93	100	107	114	121
12	200.110	89	96	103	110	117	124	131
13	200.120	99	106	113	120	127	134	141
14	200.130	110	117	123	130	137	143	150
15	200.140	121	127	134	140	146	153	159
16	200.150	132	138	144	150	156	162	168
17	200.160	143	149	154	160	166	171	177
18	200.170	155	160	165	170	175	180	185
19	200.180	167	172	176	180	184	188	193
20	200.190	181	184	187	190	193	196	199

(2) *Problem 9: What information is obtainable from a single neutrophil count?*
Given a single neutrophil count of 62, out of 100 white cells counted, what is the patient-count?

Referring to table 11, line 7, column 5, just under 60, it may be noted that, if the above count were repeated on the same or different slides until 1,000 counts were made, 954 counts would fall between 52 and 72 neutrophils (columns 3 and 7) in 100 total white cells. On line 1, 954 is the sum of 136, 341, 341 and 136. The above count of 62 was chosen because it is the first of 21 counts by

Mainland, Coady and Joseph (20) mentioned above. Their other counts ranged from 57 to 76. This is another example showing that when a sufficient number of counts are made some will fall outside the 95 per cent confidence limit. See chart 11.

DIFFERENCE BETWEEN 2 COUNTS

NEUTROPHILES

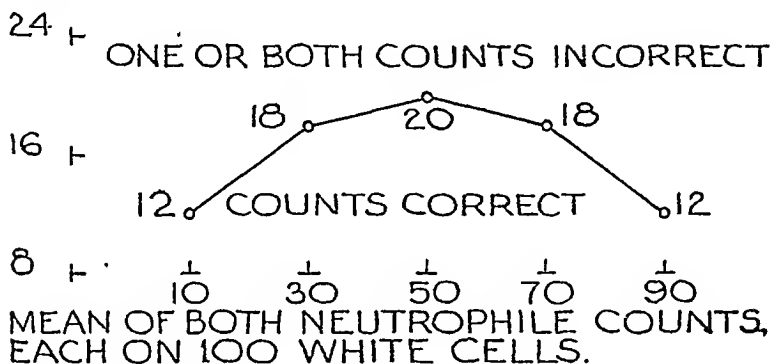


CHART 9. Neutrophil counts. To test correctness of a single neutrophil count on 2 groups, each of 100 white cells, on the same or different smears.

DIFFERENCE BETWEEN 2 COUNTS

NEUTROPHILES

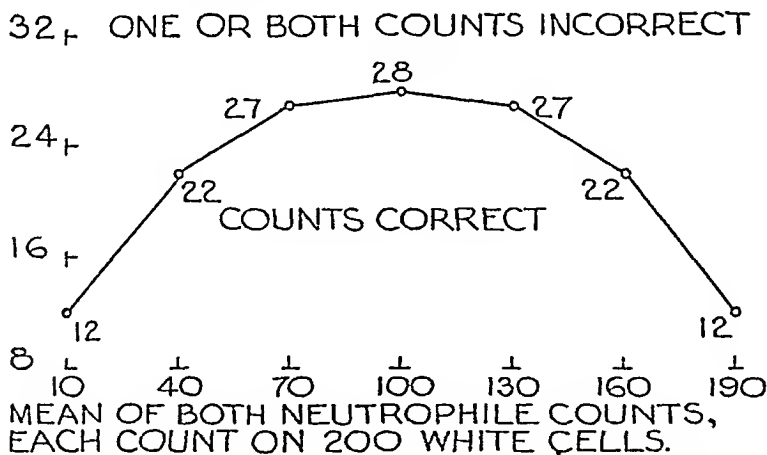


CHART 10. Neutrophil counts. To compare two counts, each on 200 white cells, on the same or different smears, from one puncture.

In their first of 20 similar counts of 200 white cells, Goldner and Mann (19) counted 95 "polymorphs." If no other counts had been made, table 12 could be used to show that out of 1,000 similar counts 682 (line 1, 341 plus 341) counts

would fall between 88 and 102 (columns 4 and 6, between lines 10 and 11). Actually their other 19 counts fell between 76 and 102 "polymorphs." See chart 12.

Medlar (23) reported 16 total and differential white cell counts on case Lo, during a period of one month. In the first count there were 68 nonsegmented neutrophils. The remaining counts ranged from 36 to 108 nonsegmented neutrophils. Can these fluctuations be produced through random sampling

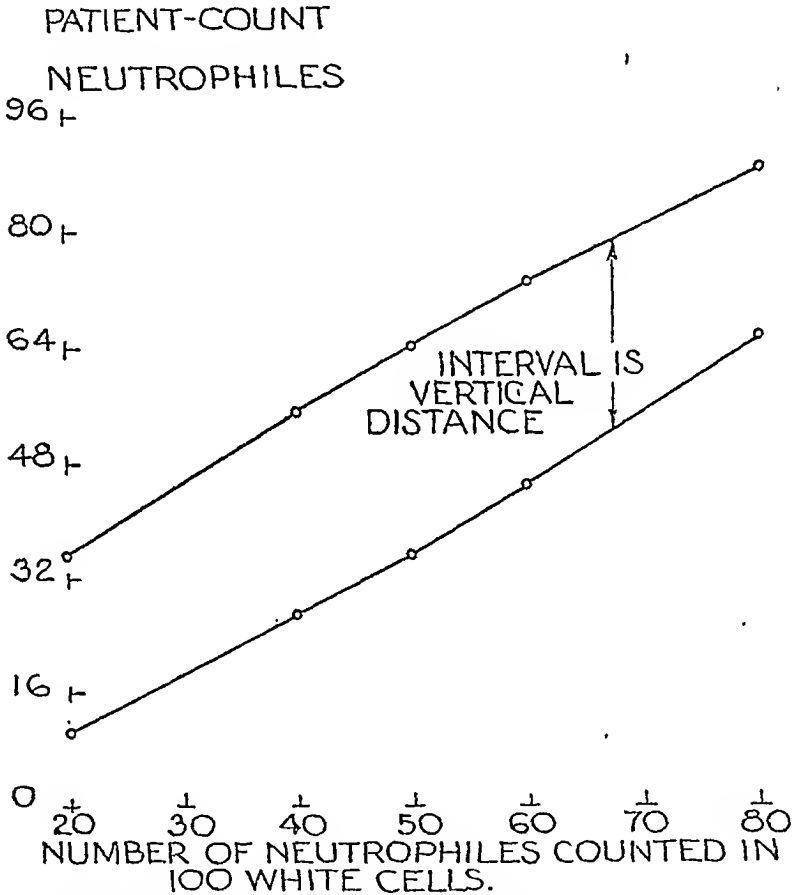


CHART 11. Neutrophil counts. To obtain the patient-count interval from a single smear-count on 100 white cells.

of the same blood? Since Medlar's total counts were 400, table 12, based on counts of 200, cannot be used directly. There is some loss of information in the following procedure, but not a serious one. By dividing the above counts by 2, they can be brought into table 12. This indicates that if only the first count of 34 nonsegmented neutrophils in 200 were available (column 5, between lines 4 and 5) other counts would fall between 19 (column 2) and 50 (column 8); provided, of course, that the blood had not changed. Subsequent counts ranging from 18 to 54 are beyond the random sampling limits. These last two figures are not on any one line in table 12, an indication that both cannot

be correctly obtained on the same blood. If table 11 were used with Medlar's counts of 400 divided by 4, the loss of information might lead to false conclusions.

Returning to problem 9, for the first mentioned count of 62 neutrophils, if no other counts are available table 11 indicates that this count could be obtained on all patients from patient 100.47 (column 8, above line 6) and patient 100.75 (column 2, above line 9). The most probable patient is patient number 100.62, whose mean neutrophil count is 62 in 100 white cells. See tables 3 and 8.

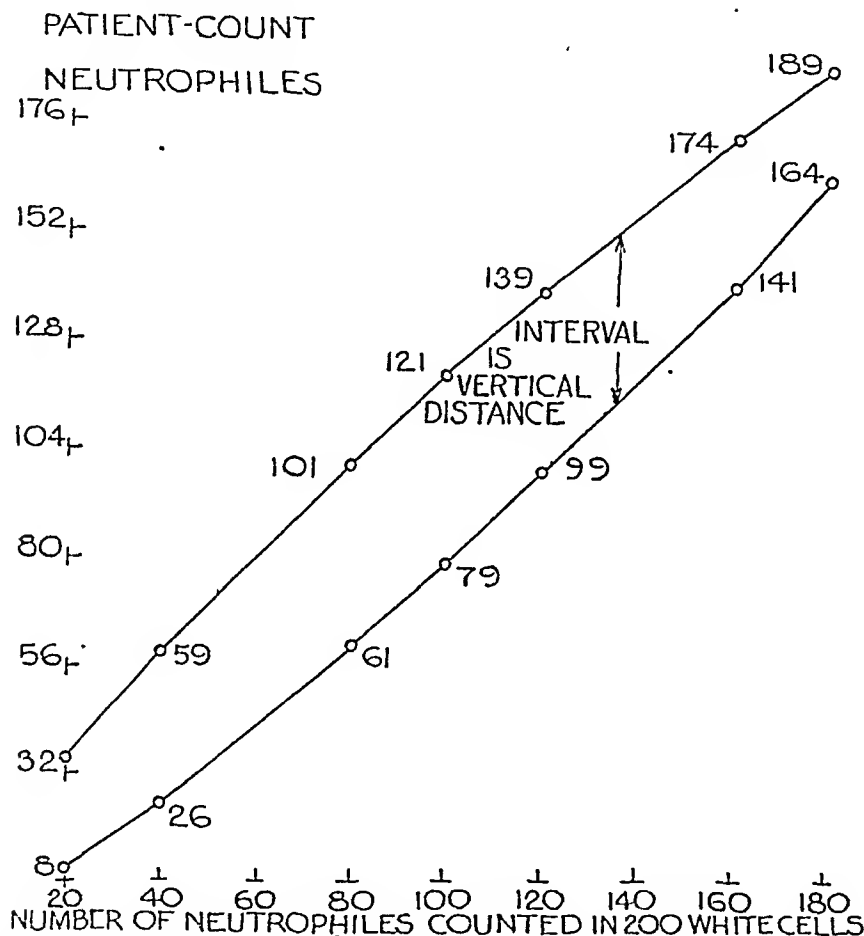


CHART 12. Neutrophil counts. To obtain the patient-count interval from a single smear-count on 200 white cells.

(3) *Problem 10: What methods may be used in determining that a single neutrophil count is correct?*

Method 1: Make two counts in 2×100 white cells. Treat difference as in problem 11. For a single neutrophil count, standing alone, none of the criteria of correct counting available for red and total white cells seems available. By making two or more counts in groups of 100 white cells, the obtained differences may be tested as provided in problem 11.

(4) *Problem 11: How large a difference between two consecutive neutrophil counts on the same blood, on the same or on different smears, may be due to random sampling?*

Method 1: Comparing an obtained difference with others in the literature. The largest difference between two differential counts of 100 on the same slide, reported by Mainland, Coady and Joseph (20), was 19 neutrophils, that is, between 57 and 76.

When making single counts of 200 on each of 20 smears, the largest difference between two consecutive counts of "polymorphs" obtained by Goldner and Mann (19) was 21, that is, between 97 and 76.

Heaf (27) sent one smear to nine competent hematologists for a differential count. Total count was not stated; range was from 75.0 to 63.3 per cent of "polymorphs." If each total count was 200, the range was 23.

TABLE 13

Ranges of samples of two

Out of 1,000 differences between two consecutive neutrophil counts on the same blood, on the same or on different smears, the number of differences shown below will exceed the indicated number of neutrophils. Differences in neutrophil counts are here assumed to be due only to random sampling. Based on Pearson (18). One total white cell count = 200.

NUMBER OF DIFFERENCES OUT OF 1,000	MEAN NUMBER OF NEUTROPHILS COUNTED IN ONE COUNT OF 200 WHITE CELLS						
	10	40	70	100	130	160	190
	Difference between two consecutive counts neutrophils						
100	7	13	16	16	16	13	7
50	9	16	19	20	19	16	9
25	10	18	21	22	21	18	10
10	11	21	25	26	25	21	11
5	12	22	27	28	27	22	12
1	14	26	31	33	31	26	14

Method 2: The difference conforms to a criterion—a table of ranges. Reading table 13: Assume that 1,000 or more differential counts of 200 have been made on patient X, and the mean number of neutrophils in one count is 100. The column headed 100 applies to the differences between consecutive counts. In one pair of counts out of 1,000 pairs, the difference will exceed 33 neutrophils. A difference greater than 16 is to be expected 100 times out of 1,000 differences. Two counts on different smears of the same blood, by Goldner and Mann (19), were 97 and 76 "polymorphs" in total counts of 200. Table 13 may be entered with the mean of the counts, 87. The difference, 21, will be exceeded about 25 times out of 1,000 differences.

Among the above-mentioned counts by Medlar (23) on case Lo were: on 5/29, 24 nonsegmented neutrophils and on the next day, 5/30, 54 nonsegmented neutrophils, both in counts of 200 (actual counts, 400). Can the difference be due to random sampling only? Entering table 13, column headed 40, (since

mean of the two counts is 39) the difference of 30 will occur less than once in 1,000 differences. The two counts are on different blood, that is, different with respect to count of nonsegmented neutrophils.

Reading table 14: This is similar to table 13, except that it is based on total counts of 100 white cells.

Among the above-mentioned counts by Mainland, Coady and Joseph (20) were 57 and 76 neutrophils on the same slide; total counts were 100 white cells. Entering table 14, column headed 70, the difference, 19, will occur about 5 times in 1,000 differences.

Method 3: Calculating from a formula, the probability that the difference could be produced by random sampling. This method was discussed by Barnett (24). Methods 2 and 4 are quicker.

TABLE 14
Ranges of samples of two

Out of 1,000 differences between two consecutive neutrophil counts on the same blood, on the same or on different smears, the number of differences shown below will exceed the indicated number of neutrophils. Differences in neutrophil counts are here assumed to be due only to random sampling. Based on Pearson (18). One total white cell count = 100.

NUMBER OF DIFFERENCES OUT OF 1,000	MEAN NUMBER OF NEUTROPHILS COUNTED IN ONE COUNT OF 100 WHITE CELLS				
	10	30	50	70	90
	Difference between two consecutive counts neutrophils				
100	7	11	12	11	7
50	8	13	14	13	8
25	10	15	16	15	10
10	11	17	18	17	11
5	12	18	20	18	12
1	14	21	23	21	14

Method 4: Can a population be found (tables 11 and 12) from which both counts were probably drawn? When two neutrophil counts can be found on one line in table 11 or 12, they are obtainable from the same blood. The difference is due to random sampling. Counts on the same blood should not be separated by more than 3 line-intervals or standard deviations. If the separation is greater, the probability that both counts were correctly obtained on the same blood is so small as to justify their use with reserve. Usually, two correct counts can be found on several lines, or vertical intervals, close to each other. (Charts 11 and 12.) In the absence of other information, one line is as good as another.

Example 1: Two counts mentioned above, 57 and 76 (Mainland, Coady and Joseph (20)), may be found on lines 7 and 8, table 11. Being separated by 4 line-intervals, one may conclude that one or both counts were not correctly obtained on the same blood; or that the difference, 19, was produced only by random sampling, although the probability is small.

Example 2: Two counts mentioned above, of 24 and 54 nonsegmented neutrophils, by Medlar (23) can be found on line 5, table 12. Being separated by almost 6 line-intervals, the probability that both counts were obtained on the same blood is about two in one million. The reasonable conclusion is that the blood changed.

(5) *Problem 12: Are two neutrophil counts better than one?* If two differential counts, each on 100 white cells, are made, their difference may be tested on a range table such as table 14. By finding both counts on one line in table 11, their distance from each other in terms of line-intervals (standard deviations) may be obtained, together with the patients that might furnish the counts.

V. THE LYMPHOCYTE AND MONOCYTE COUNTS

When making a differential count on 100 white cells, tables 11 and 14 may be used for any type of cell, provided the type number be 10 or more.

An example from Mainland, Coady and Joseph's (20) counts: in 100 white cells on different smears of the same blood there were 35 and 23 lymphocytes. Referring to table 14, column headed 30, the difference—their largest—of 12 will be exceeded about 75 times in 1,000 pairs of counts. Random sampling accounts for the difference. This is confirmed by referring to table 11. The mean of the two counts, 30 practically, is located in column 5, on line 4. The two counts are separated by approximately 2 line-intervals.

When making a differential count on 200 white cells, tables 12 and 13 may be used for any type of cell, provided the type number be 10 or more.

Among Goldner and Mann's (19) lymphocyte counts on 200 white cells were 113 and 82, on different smears of the same blood. Entering table 13, column headed 100 (100 being close to the mean of 113 and 82), the difference, 31 lymphocytes, will be exceeded through random sampling about 3 times in 1,000 pairs of counts. This is confirmed by referring to table 12, line 11. The counts are separated by approximately 4 1/2 line-intervals. (See problem 3, method 3.)

VI. SMALL PERCENTAGE COUNTS—LESS THAN 5 PER CENT

Reading table 15: The table may be used regardless of whether the total count is 100 or 400 white cells, or any other number. When a count is a small-proportion count, its variation through random sampling is shown in the lower and upper limits in the table. When a count falls beyond these limits one may suspect a change in the blood, or error. The use of the table is shown in two examples.

Example 1: Medlar (23) published 17 total and differential counts on case Sch. In the first of these there were 12 eosinophils in a total count of 400. If on this day, 5/12, 100 similar counts had been made, what variation in eosinophil count could be expected?

Locating the number of cells counted, 12, in the first column of table 15, 99 out of 100 similar counts would range from 5 to 24. Between 5/12 and 6/17,

all 17 counts ranged from 10 to 26 eosinophils, indicating no change in the blood with regard to eosinophils.

Example 2: In their first differential count on student number 24 (Mainland, Coady and Joseph (20)) were 3 monocytes in a total count of 100 white cells. What will other counts be, if they vary only through random sampling? Loca-

TABLE 15

Adaptation of Ricker's (28) table of confidence limits for Poisson frequency distributions

NUMBER OF CELLS COUNTED, OF ONE TYPE	OUT OF 100 SIMILAR COUNTS, 99 WILL FALL BETWEEN THE LIMITS BELOW	
	Lower limit	Upper limit
0	0.0	5
1	0.0	7
2	0.1	9
3	0.3	11
4	0.6	13
5	1.0	14
6	1.5	16
7	2.0	17
8	2.5	19
9	3.1	20
10	3.7	21
11	4.3	23
12	4.9	24
13	5.5	25
14	6.2	27
15	6.8	28
16	7.5	29
17	8.2	31
18	8.9	32
19	9.6	33
20	10.3	35
21	11.0	36
22	11.8	37
23	12.5	38
24	13.2	40
25	14.0	41

ting 3, in the first column of table 15, out of 100 similar counts 99 will range from 0 to 11. Their next 20 counts ranged from 1 to 8 monocytes.

CONCLUSIONS

Red Cells Counts on 80 Squares

A test of correctness of a single count: Record separately the counts on 5 groups of 16 squares. If the total count is 100, random streaming can produce a differ-

ence between the largest and smallest counts that will exceed 19 red cells in 10 out of 1,000 counts, each totaling 100. The difference will exceed 20 red cells, in 5 out of 1,000 similar counts. For count 700, corresponding differences are 50 (at 10/1000 level) and 53 red cells.

For all intermediate counts, straight line interpolation may be used, unless otherwise stated.

Example: For count 400, a difference exceeding 40 red cells (5/1000 level) may lead to the conclusion that the difference includes error.

To compare two counts in one filling of the counting chamber: If the mean of both counts is 100, random streaming can produce a difference between them that will exceed 36 red cells, in 10 out of 1,000 differences obtained on mean counts of 100. The difference will exceed 40, in 5 out of 1,000 similarly obtained differences. For a pair of counts with mean equal to 700, corresponding differences are 96 and 105 red cells.

Example: For a pair of counts with mean equal to 400, that is, 440 and 360, a difference exceeding 79 red cells (5/1000 level) would be presumed to include error.

To compare two counts from one puncture, but with different pipets and chambers: If the mean of both counts is 100, random sampling can produce a difference between them that will exceed 41 red cells in 10 out of 1,000 differences obtained on mean counts of 100. The difference will exceed 45 red cells in 5 out of 1,000 similarly obtained differences. For a pair of counts with mean equal to 700, corresponding differences are 189 and 207 red cells.

Example: For a pair of counts with mean equal to 400, that is, 465 and 335, a difference exceeding 127 red cells (5/1000 level) may be presumed to include error.

The mean of 2 counts cannot be depended upon to furnish a better estimate of the patient-count than either count alone.

To obtain the patient-count interval from a single chamber-count: Multiply the count by 1.31 (131 per cent), then by 0.80 (80 per cent). The interval contains the patient-count with close to 99.6 per cent confidence coefficient. Although the most probable patient-count is the chamber-count, the two seldom coincide.

Example: A chamber-count of 400 red cells may be interpreted: the patient-count is between 3.2 and 5.24 million.

White Cell Counts on 4 Square Millimeters

A test of correctness of a single count: Record separately the counts on 4 squares, each 1 square millimeter. If the total is 50 white cells, random streaming can produce a difference between the largest and smallest counts that will exceed 16 white cells in 10 out of 1,000 counts, each totaling 50. The difference will exceed 17 white cells in 5 out of 1,000 similar counts. For a total count of 400, corresponding differences are 44 and 47 white cells.

Example: For a total count of 200, a difference exceeding 33 white cells (5/1000 level) may be presumed to include error.

To compare two counts in one filling of the counting chamber: If the mean of

both counts is 50, random streaming can produce a difference between them that will exceed 26 white cells in 10 out of 1,000 differences obtained on mean counts of 50. The difference will exceed 28 white cells in 5 out of 1,000 similar differences. If the mean of both counts is 400, corresponding differences are 73 and 79 white cells.

Example: For a pair of counts with mean equal to 200, that is, 229 and 171, a difference exceeding 56 white cells (5/1000 level) would be presumed to include error.

To compare two counts from one puncture, but with different pipets and chambers: If the mean of both counts is 50 white cells, random sampling can produce a difference between them that will exceed 28 white cells in 10 out of 1,000 differences obtained on mean counts of 50. The difference will exceed 31 in 5 out of 1,000 similarly obtained differences. If the mean of both counts is 400, corresponding differences are 120 and 131.

Example: For a pair of counts with mean equal to 200, that is, 239 and 161, a difference exceeding 77 white cells (5/1000 level) may be presumed to include error.

To obtain the patient-count interval from a single chamber-count: If the chamber-count is 100, multiply the count by 1.47, then by 0.71. The interval contains the patient-count, with close to 99.6 per cent confidence coefficient. Intervals for other counts are: for 200, 1.37 to 0.76; for 300, 1.33 to 0.78; for 400, 1.31 to 0.79.

Example: A chamber-count of 150 may be interpreted: the patient-count is between 10,650 and 5,513 white cells. The most probable patient-count is 7,500.

Neutrophil Count

A test of correctness of a single neutrophil count: Record separately the counts on two groups, each of 100 white cells, on the same or different smears from one puncture. If the mean of both counts is 10 neutrophils, random sampling can produce a difference between them that will exceed 11 neutrophils in 10 out of 1,000 differences obtained on mean counts of 10. When mean counts are 30, 50, 70, 90 neutrophils, corresponding differences are 17, 18, 17, 11. Increase these differences by 1 to obtain the 5/1000 level.

Since the maximum difference is for 50 per cent neutrophils, straight line interpolation for intermediate counts may be used for short distances only and, in no case, across a 50 per cent value.

Example: 57 and 76 neutrophils were counted on the same slide. The difference, 19, is at the 5/1000 level.

If two neutrophil counts are made, each on 200 white cells, the differences between them for means of 10, 40, 70, 100, 130, 160, 190 neutrophils are, respectively, 11, 21, 25, 26, 25, 21, 11, at the 10/1000 level. Increase these differences by 2 to obtain the 5/1000 level. Interpolation as above.

To obtain the patient-count interval from a single smear-count on 100 white cells: If the smear-count is 20 neutrophils, the patient-count lies within 11 to

35, with close to 99.6 per cent confidence coefficient. Intervals, in parentheses, follow other counts. For 40 (27 to 55); for 50 (35 to 64); for 60 (45 to 73); for 80 (66 to 89).

To obtain the patient-count interval from a single smear-count on 200 white cells: For count 20, the patient-count lies within the interval 11 to 36 neutrophils. Intervals, in parentheses, follow other smear-counts. For 40 (26 to 59); for 80 (61 to 101); for 100 (79 to 121); for 120 (99 to 139); for 160 (141 to 174); for 180 (164 to 189).

Remaining Differential Counts

The above data on neutrophil counts may be used for all other differential counts, by replacing the word "neutrophil" with lymphocyte, monocyte, non-segmented neutrophil, etc., so long as the differential count exceeds 5 per cent of the total count.

For counts less than 5 per cent, Ricker's table of confidence limits for Poisson frequency distributions may be used, regardless of whether the total count is 100 or several hundred.

CONCLUSIONES

Eritrocitometrías en 80 Cuadrados

Comprobación de la exactitud de una sola numeración: Anótense por separado las numeraciones ejecutadas en 5 grupos de 16 cuadrados. Si el total representa 100, los cotejos al azar pueden revelar una diferencia entre las numeraciones máxima y mínima que excederá de 19 eritrocitos en 10 de cada 1,000 numeraciones, cada una de las cuales representa 100 glóbulos. La diferencia excederá de 20 en 5 de cada 1,000 numeraciones semejantes. Para 700 las diferencias correspondientes son 50 (al nivel de 10/1000) y 53 glóbulos rojos.

Para todas las numeraciones intermedias puede utilizarse la interpolación en línea recta, a menos que se diga otra cosa.

Ejemplo: Para una numeración de 400, una diferencia que exceda de 40 glóbulos rojos (nivel de 5/1000), puede llevar a la conclusión de que la diferencia comprende el error.

Para comparar dos numeraciones en una repleción del hematómetro: Si el promedio de ambas numeraciones representa 100, las numeraciones al azar pueden producir una diferencia entre ellas que excederá de 36 glóbulos rojos en 10 de cada 1,000 diferencias obtenidas en numeraciones medias de 100. La diferencia excederá de 40 en 5 de cada 1,000 diferencias obtenidas en forma semejante. Para un par de numeraciones cuyo promedio represente 700, las diferencias correspondientes representan 96 y 105 glóbulos rojos.

Ejemplo: Para un par de numeraciones con un promedio equivalente a 400, es decir, 440 y 360, toda diferencia que exceda de 79 glóbulos rojos (nivel de 5/1000), puede suponerse que comprende el error.

Para comparar dos numeraciones de una punción, pero con diferentes pipetas y hematómetros: Si el promedio de ambas numeraciones representa 100, las numeraciones al azar pueden producir una diferencia entre ellas que excederá

de 41 glóbulos rojos en 10 de cada 1,000 diferencias obtenidas en numeraciones medias de 100. La diferencia excederá de 45 en 5 de cada 1,000 diferencias obtenidas en forma semejante. Para un par de numeraciones que promedien 700, las diferencias correspondientes representan 189 y 207 glóbulos rojos.

Ejemplo: Para un par de numeraciones con un promedio equivalente a 400, es decir, 465 y 335, toda diferencia que exceda de 127 glóbulos rojos (nivel de 5/1000), puede suponerse que comprende el error.

No puede confiarse en que el promedio de dos numeraciones arroje un cálculo más exacto de la hematimetría del enfermo, que una sola numeración.

Para obtener el intervalo-numeración del enfermo por una sola numeración del hemátmetro: Multiplíquese la numeración por 1.31 (131 por ciento), y después por 0.80 (80 por ciento). El intervalo contiene la numeración del enfermo con una exactitud casi de 99.6 por ciento. Aunque la numeración del enfermo más aproximada es la del hemátmetro, las dos rara vez coinciden.

Ejemplo: Una numeración de hemátmetro de 400 glóbulos rojos, puede interpretarse así: la numeración del enfermo es entre 3.2 y 5.24 millones.

Leucocitometrías en 4 mm. Cuadrados

Comprobación de la exactitud de una sola numeración: Anótense por separado las numeraciones ejecutadas en 4 cuadrados, cada uno de 1 mm. cuadrado. Si el total representa 50 leucocitos, los cotejos al azar pueden revelar una diferencia entre las numeraciones máxima y mínima que excederá de 16 leucocitos en 10 de cada 1,000 numeraciones, cada una de las cuales representa 50 glóbulos. La diferencia excederá de 17 en 5 de cada 1,000 numeraciones semejantes. Para 400 las diferencias correspondientes son 44 y 47 leucocitos.

Ejemplo: Para una numeración total de 200, toda diferencia que exceda de 33 leucocitos (nivel de 5/1000), puede llevar a la conclusión de que la diferencia comprende el error.

Para comparar dos numeraciones en una repleción del hemátmetro: Si el promedio de ambas numeraciones representa 50, las numeraciones al azar pueden producir una diferencia entre ellas que excederá de 26 leucocitos en 10 de cada 1,000 diferencias obtenidas en numeraciones de 50. La diferencia excederá de 28 en 5 de cada 1,000 diferencias obtenidas en forma semejante. Para un par de numeraciones que promedien 400, las diferencias correspondientes representan 73 y 79 leucocitos.

Ejemplo: Para un par de numeraciones con un promedio equivalente a 200, es decir, 229 y 171, toda diferencia que exceda de 56 leucocitos (nivel de 5/1000), puede suponerse que comprende el error.

Para comparar dos numeraciones de una punción, pero con diferentes pipetas y hemátmetros: Si el promedio de ambas numeraciones representa 50, las numeraciones al azar pueden producir una diferencia entre ellas que excederá de 28 leucocitos en 10 de cada 1,000 diferencias obtenidas en numeraciones medias de 50. La diferencia excederá de 31 en 5 de cada 1,000 diferencias obtenidas en forma semejante. Para un par de numeraciones cuyo promedio equivalga a 400, las diferencias correspondientes representan 120 y 131.

Ejemplo: Para un par de numeraciones con un promedio equivalente a 200,

es decir, 239 y 161, toda diferencia que exceda de 77 leucocitos (nivel de 5/1000), puede suponerse que comprende el error.

Para obtener el intervalo-numeración del enfermo por una sola numeración del hemátmetro: Si la numeración da 100, multiplíquese por 1.47, y después por 0.71. El intervalo contiene la numeración del enfermo con una exactitud casi de 99.6 por ciento. Los intervalos para otras numeraciones son: para 200: 1.37 a 0.76; para 300: 1.33 a 0.78; para 400: 1.31 a 0.79.

Ejemplo: Una numeración hematimétrica de 150 leucocitos, puede interpretarse así: la numeración del enfermo queda entre 10,650 y 5,513 leucocitos. La más probable es 7,500.

Numeración de Neutrófilos (Neutrofilometrías)

Comprobación de la exactitud de una sola numeración: Anótense por separado las numeraciones ejecutadas en 2 grupos, cada uno de 100 leucocitos, en el mismo o diferentes frotos de una punción. Si el promedio de ambas numeraciones representa 10 neutrófilos, los cojetos al azar pueden revelar una diferencia entre ellas que excederá de 11 neutrófilos en 10 de cada 1,000 diferencias obtenidas en numeraciones medias de 10. Cuando las numeraciones medias representan 30, 50, 70, 90 neutrófilos, las diferencias correspondientes son 17, 18, 17, 11. Auméntense estas diferencias en 1 para obtener el nivel de 5/1000.

Toda vez que la diferencia máxima es para 50 por ciento de neutrófilos, sólo puede utilizarse la interpolación para numeraciones intermedias en distancias cortas, y en ningún caso más allá de un valor de 50 por ciento.

Ejemplo: Se contaron 57 y 76 neutrófilos en la misma placa. La diferencia, 19, se halla al nivel de 5/1000.

Para un par de numeraciones, cada una de 200 leucocitos, las diferencias entre ellas en promedios de 10, 40, 70, 100, 130, 160, 190 neutrófilos son, respectivamente, 11, 21, 25, 26, 25, 21, 11, al nivel de 5/1000. Auméntense estas diferencias en 2 para obtener el nivel de 5/1000. Se hace la interpolación según se describe más arriba.

Para obtener el intervalo-numeración del enfermo por una sola numeración-frote en 100 leucocitos: Si la numeración-frote representa 20 neutrófilos, la numeración del enfermo queda entre 11 a 35, con una exactitud casi de 99.6 por ciento. Los intervalos, en paréntesis, siguen otras numeraciones. Para 40: (27 a 55); para 50: (35 a 64); para 60: (45 a 73); para 80: (66 a 89).

Para obtener el intervalo-numeración del enfermo por una numeración-frote en 200 leucocitos: Para una numeración de 20, la numeración del enfermo queda en el intervalo entre 11 a 36 neutrófilos. Los intervalos, en paréntesis, siguen otras numeraciones-frotos. Para 40: (26 a 59); para 80: (61 a 101); para 100: (79 a 121); para 120: (99 a 139); para 160: (141 a 174); para 180: (164 a 189).

Otras Numeraciones Diferenciales

Los datos anteriores acerca de las neutrofilometrías rezan con todas las demás numeraciones diferenciales, cambiando la palabra "neutrófilo" a linfocito, monocito, neutrófilo no segmentado, etc., siempre que la numeración diferencial exceda de 5 por ciento de la numeración total.

Para numeraciones inferiores a 5 por ciento, puede utilizarse la tabla de límites de exactitud de Ricker para las distribuciones de frecuencia de Poisson, ya represente la numeración total 100 o varios centenares.

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PLEURAL SHOCK AND CEREBRAL EMBOLISM¹

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Pleural puncture employed either in pneumothorax therapy, aspiration of an empyema cavity or in exploratory thoracocentesis may result in a series of signs and symptoms which have been usually classified as pleural shock or cerebral embolism.

LITERATURE

Pleural shock, so-called, was originally described by Roger (16) in 1864. He described it as an "eclamptic fit" characterized by cardiorespiratory embarrassment, tonic and clonic contraction of the muscular system, loss of consciousness and, in some instances, sudden death.

Besnier (2) also agreed with Roger that these attacks were of nervous origin due to irritation of sensitive nerve fibres in the pleura, which in turn transmitted this irritation to the central nervous system.

Cordier (8), a believer in the theory of pleural shock, reported in 1910 that the injection of iodine into the pleural cavity of a rabbit caused convulsions and death. If the vagus nerves were cut, this did not occur.

Forlanini (10, 11), the father of pneumothorax therapy, maintained that these accidents were due to pleural shock or eclampsia and held that cerebral embolism did not occur. In 10,000 punctures on 134 patients he had 12 accidents, 5 with temporarily serious conditions, but all with final recovery.

Authors of the other school of thought believe that this syndrome of pallor, nausea, vertigo, convulsive tremors, coma, paralysis and temporary blindness is due to cerebral embolism. They maintain that the mechanism of gas embolism is brought about by the introduction of air into the systemic arteries by way of the left heart from the pulmonic veins. Air may enter these veins from three sources: the alveolar air, the intrapleural air or the air in the pneumothorax apparatus. This may be produced by the puncturing of a vein or indirectly through injury of the visceral pleura or lung tissue. If the needle punctures the lung, because of fibrous adhesions or other pathological changes, the tissue is unable to contract and seal the opening immediately with the result that air is aspirated into the pulmonic vessels. Due to the subatmospheric pressure in the veins, air is sucked into the lumen, especially if high pressures are employed in the pneumothorax. When normal lung parenchyma is injured, the blood vessels are capable of reducing their size and their lumina so quickly that little or no air is admitted.

Brauer (5) in 1912 was the first to recognize the danger of air embolism in thoracic work and rejected the opinion held by Roger and others as to these so-called pleural reflexes.

Brandes (4) in 1912 published the report of a case in which he tried to outline the extent of an empyema cavity by an injection of bismuth paste through the sinus. The rubber catheter apparently injured the wall of the cavity. Most of the bismuth escaped alongside of the catheter. The patient had a spasm, with deviation of the eyes and died after twenty hours. At autopsy, bismuth was found in the smallest blood vessels of the cerebral

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cortex of both hemispheres. On examination of serial sections from the wall of the sinus, the bismuth could be traced up to the pulmonary capillaries and veins.

Croizier (9) was convinced that this symptom complex was due to cerebral embolism. He repeated the experiments of Cordier but controlled them by manometric readings. He induced the convulsions, crises and death described by Cordier only when the iodine was injected into the lung tissue itself. Administration of iodine and other irritants into the pleural cavity occasionally caused immediate shock, but did not bring about convulsions or death.

Wever (18) demonstrated, by numerous experiments on rabbits, dogs and cats, the effects of introducing air directly into the carotid arteries and found that the symptom complex coincides with that sometimes encountered in pleural puncture. Depending on the amount of air introduced, he observed variations from mild tremors or mild disturbances of cardiac and respiratory actions to sudden death.

Many physicians still diagnose cases which present this symptom complex and go on to complete recovery as pleural shock. We have always maintained that the symptom complex characterized by pallor, sudden changes in respiration and circulation, dizziness, dilated pupils, cyanosis, tonic and clonic convulsions, paralysis, loss of consciousness, and sometimes death, is caused by cerebral embolism and not pleural shock. The features of the clinical picture of cerebral embolism following pleural puncture are so varied that it is quite impossible to classify them. Besides changes in respiration and circulation the majority of cases present varying degrees of clonic or tonic convulsions, paralysis and ocular disturbances.

The clonic and tonic convulsions with subsequent paralysis are due to nutritive changes in the motor area of the cortex. The pupils are usually dilated and fail to react to light. Strabismus may be present. The ophthalmoscopic examination of the retinal vessels for the presence of air bubbles is of the greatest diagnostic importance. In cases with ocular changes, if examination of the eye grounds is negative, the source of the embolism may lie in the occipital lobe. Excessive damage to the vital centres of respiration in the medulla oblongata may result in sudden death. In cases of death following this dreaded complication, an autopsy should be performed as soon as possible to eliminate any postmortem changes in the brain. At times it is impossible to obtain pathologico-anatomical proof in fatal cases of air embolism because of the fact that minimal air bubbles introduced into the carotid arteries often cause sudden death.

Chaubaud (7) divided his cases into several groups, syncopal, convulsive and paralytic. He found that the syncopal form included 20 per cent of the cases with 80 per cent mortality. The convulsive and paralytic forms included 80 per cent of the cases with 50 per cent mortality.

Cerebral embolism was a comparatively frequent accident when Forlanini and his followers did pioneer work in pneumothorax. No manometer was employed and often air was injected at high pressures. With the introduction of the manometer by Saugmann this complication has certainly become somewhat less frequent.

Saugmann (17), in a series of 215 initial pneumothoraces and 5,500 follow-up treatments, reported 2 cases of cerebral embolism.

Matz (15) encountered the condition 18 times in a series of 588 treatments.

Bruns (6) reported 16 cases of cerebral embolism with 7 deaths in a series of 12,700 pneumothoraces.

Andrews (1) in a series of 8,528 pleural punctures reported 6 cases with 2 fatalities.

At the Boston Sanatorium, during the past fifteen years, in a series of 90,120 pleural punctures employed mostly in pneumothorax work, we have encountered 12 cases of

cerebral embolism and, of these, 3 were fatal. One of the fatal cases, no. 12, we believe died of novocaine poisoning and not from cerebral embolism as was thought at first.

Jessen (13) in 1913 reported a similar case in which he was attempting to anesthetize the pleura prior to performing a thoracoplasty. In the process of the novocaine infiltration anesthesia the patient had an attack of coughing, became cyanotic, unconscious and died within sixteen hours. At autopsy no air could be found in the cerebral vessels.

Macfie (14) in 1928 reported a case of novocaine poisoning during the injection of the pleura before a pneumothorax treatment. This case was definitely substantiated by Sir William Willcox.

Jaquet (12) states that he has witnessed 2 fatalities following the injection of novocaine. The first fatality occurred after the injection of 1 cc. of a 1 per cent solution of novocaine at the base of a hemorrhoid preparatory to a hemorrhoidectomy. The patient went into a state of collapse and expired within ten minutes. The second fatality occurred after the injection of about 1 cc. of a 1 per cent solution of novocaine into the superior laryngeal nerve for the relief of pain in a case of tuberculous laryngitis. The patient went into a state of collapse and expired within twenty minutes.

Blumer (3) maintains that toxic reactions to novocaine vary considerably in different persons. In general, there are two types of serious reactions. In the first type the patient falls dead before the physician has time to realize what has happened. The patient becomes pale, collapses, gasps for breath and dies. It is likely that in such a case there has been rapid absorption which is toxic to the heart and that death is essentially cardiac. In the second variety of reaction there is evidence of central stimulation. The events occur more slowly, but even here the symptoms can develop rapidly and lead to death before the physician appreciates their seriousness. The patient becomes restless, anxious, excited and may become delirious. The pulse is weak and irregular and the respirations rapid. Convulsions may also appear. There is evidence of sympathetic overactivity for the skin is pale and the pupils dilated. Finally the dyspnea becomes marked and cyanosis develops. Unconsciousness results and death occurs in coma or convulsions. The course of events described may take only a few minutes or extend over several hours. There are a number of milder reactions to local anesthetics based on personal idiosyncrasy. These are not alarming but the patient should be closely watched.

The local anesthetics are rapidly destroyed in the body by the liver and if one can maintain the respiration until the concentration of the drug has been reduced below the toxic level the patient can often be saved.

In the sudden type of death from cardiovascular collapse the physician is handicapped. The patient usually is dead before anything can be done.

In those cases where the symptoms are more gradual in onset, definite help can be rendered. Treatment consists in the administration of artificial respiration if the breathing is feeble or has ceased. Then a soluble barbiturate should be injected intravenously in sufficient dose to stop convulsions or if the latter are not present to put the patient to sleep.

OBSERVATIONS

At the Boston Sanatorium we appreciate the hazards of novocaine infiltration anesthesia. Consequently it is employed in a 1 per cent solution and only for the initial pneumothorax treatment and not for subsequent refills. We also stress the importance of pulling back on the piston of the syringe during the novocaine injection so as to avoid the danger of injecting the drug into a vein.

In the past ten years one of the writers (J. B. A.), in a series of over 10,000 pleural punctures employed in pneumothorax work, thoracocentesis and pneumonolyses, has been fortunate in having had only one case of cerebral embolism (case 11).

At the Boston Sanatorium in a series of about 700 intrapleural pneumonolyses and thoracoscopic examinations, both with and without manipulation of the visceral pleura, we have never observed a case of so-called pleural shock or air embolism.

If such a mechanism of pleural reflexes existed, the mechanical and thermal stimulation of intrapleural pneumolysis should certainly produce pleural shock. Apparently, the absence of the symptom-complex in these cases is due to the fact that the visceral pleura is not damaged which might allow chances for air embolism to occur.

In the prevention of cerebral embolism careful technique is of extreme importance. We have always placed great emphasis upon the mental attitude of the patient. The preoperative administration of a sedative is advocated. We recommend the use of novocaine in all cases of initial pneumothorax. Inasmuch as cerebral embolism occurs more frequently at the first attempt at artificial pneumothorax, the patient should receive his treatment not in the operating room but at the bedside. In this way the patient might be kept lying flat with his head lowered while the treatment is being given. With the head in this position, in case of cerebral embolism the air bubbles do not have a tendency to reach the capillaries of the brain.

The site of puncture should be away from the area of disease. All possible injury to the lung and pleura should be avoided.

Air should not be introduced until definite subatmospheric manometric reading is obtained and definite oscillations are present. The location of the needle should be known at all times during the procedure. Every case should be fluoroscoped frequently so that the operator is well acquainted with the amount of collapse that is present. We have never seen a case of cerebral embolism in a patient with a good collapse.

Patients with adhesions should always be approached cautiously and only after careful physical and X-ray study. Of course, it must be admitted that cerebral embolism, especially during the initial pneumothorax induction, cannot be prevented in every case since one cannot tell by X-ray study whether or not the lung that we intend to collapse is adherent.

No one will deny that the needle injures the adherent lung without our knowledge in a very high percentage of cases during the initial pneumothorax induction. It is indeed a fortunate coincidence that cerebral embolism does not occur more frequently.

When cerebral embolism occurs the operation should be stopped immediately and the patient's head lowered if it is not already so. The cardiac action should be reinforced with stimulants such as adrenaline hydrochloride, coramine or caffeine sodium benzoate. We should concentrate on strengthening the heart action and increasing the blood flow through the brain in order to force the air

bubbles from the capillaries in the brain, as soon as possible, and drive them to the lungs. Morphia should not be employed as it is a respiratory depressant.

When confronted by cerebral embolism the clinical signs during the attack will give a fairly practical indication of the extent of the lesion. If the patient survives the first attack, the outlook is good, and he will gradually recover from all the bad effects of the accident. In the great majority of cases all the symptoms are temporary.

The ultimate prognosis in any case of cerebral embolism following pleural puncture depends upon the amount of air entering the blood-stream and upon the region of the brain which is most seriously damaged.

The object of this paper is to emphasize the risk of introducing a needle into a diseased lung. The confusion which exists between the two schools of thought, namely pleural shock and cerebral embolism, tends to give a false notion concerning the seriousness of this complication. From our experience, we believe that pleural shock is rare and may occur in very excitable and neurotic patients, but the symptom-complex of cyanosis, changes in respiration and circulation, convulsions, ocular disturbances, loss of consciousness, aphasia, paralysis, and sometimes death, occurring during pleural puncture is definitely due to cerebral embolism.

CASE HISTORIES

Case 1: F. L., male, age 48, was admitted with a history of cough, expectoration, weakness and loss of weight. The sputum was positive for tubercle bacilli. Roentgenogram revealed bilateral infiltration with cavitation at the right top.

Right pneumothorax was advised. During the initial treatment, after the injection of about 50 cc. of air, the patient went into a state of collapse. He became pulseless, cyanotic and developed tonic and clonic convulsive movements of both arms and legs. His pupils became widely dilated and his respirations were quite feeble. The blood pressure was 90/60. Coramine was immediately injected and the patient responded quite well. Air bubbles were seen in the retinal vessels. He developed a left-sided hemiplegia. The use of his left arm and leg returned at the end of eight days.

Five months later he left the hospital against advice.

Case 2: B. S., female, age 28, was admitted with a history of cough, expectoration, loss of weight and frequent colds. The sputum was positive for tubercle bacilli. Roentgenogram revealed bilateral infiltration with cavitation at the left top.

Left pneumothorax was advised and during the initial treatment, after the injecting of 100 cc. of air, the patient went into collapse. She became pulseless, cyanotic and had several tonic and clonic convulsive movements. Her pupils were slightly dilated. Coramine was immediately given and the patient made a complete recovery in twenty minutes. No air bubbles could be seen in the retinal vessels.

Two days later, left pneumothorax was successfully instituted and the patient obtained a good collapse. Her sputum became negative and she was discharged.

Case 3: S. G., male, age 37, was admitted with a history of cough and blood-streaked sputum. The sputum was positive for tubercle bacilli. Roentgenogram revealed bilateral infiltration with cavitation in the right upper lobe.

Right pneumothorax was advised. Ten treatments were administered in which about 200 cc. of air were injected each time. Fluoroscopic examination showed a fairly good anterior-posterior collapse of the right lung but poor lateral collapse. During the eleventh treatment, after the injection of 75 cc. of air, the patient went into a state of collapse. He became cyanotic and pulseless. The respirations were weak, the pupils widely dilated and there was rigidity of both upper and lower limbs. Coramine was immediately given and the patient responded well. No air bubbles could be seen in the retinal vessels. After two days, the vision which was blurred at the time of the attack had cleared up and the stiffness of the limbs had disappeared, with the exception of the left leg which is still somewhat rigid even to-day, two years following the cerebral accident.

The patient made an uneventful recovery and with continued bed-rest his sputum became negative and he was discharged.

Case 4: H. C., female, age 30, was readmitted because of occasional streaking. Her sputum was positive for tubercle bacilli. On her previous admission she had been treated by bilateral pneumothorax and bilateral intrapleural pneumonolyses. Roentgenogram revealed bilateral partial pneumothorax. The collapse on the right side was more satisfactory than on the left.

During the first refill on the left side, while the operator was trying to obtain a manometric reading, the patient went into collapse, became cyanotic and pulseless. The respirations became very feeble and she had several tonic and clonic convulsions. Coramine was immediately given and in two minutes the patient was dead. No air bubbles could be seen in the retinal vessels. The blood pressure was 80/60.

A postmortem examination performed twelve hours later showed the presence of a bilateral pneumothorax with adhesive pleuritis on the left side. A small puncture wound was found in the left pleural cavity. No air was detected in the cerebral vessels.

Case 5: F.F., male, age 49, was admitted with a history of slight cough, loss of appetite and weight, weakness and dyspnea. The sputum was positive for tubercle bacilli. Roentgenograms revealed a decrease in radiability of the right lower lung field consistent with fluid and slight infiltration of the left top. On thoracocentesis of the left chest, 1,000 cc. of straw-colored fluid was aspirated. This procedure was performed about once monthly.

This fluid eventually became thick and it was impossible to aspirate it. After ten such treatments it was decided to aspirate by catheter method. During the latter process, while the catheter was being inserted, the patient collapsed, became cyanotic, pulseless, had tonic and clonic convulsions and developed a right-sided hemiplegia. The pupils were widely dilated. Adrenaline was immediately given and the patient's condition gradually improved. No air bubbles could be detected in the retinal vessels. In ten days the patient had made a complete recovery. Two months later, because of marked dyspnea, a thoracotomy was performed. About one inch of the ninth and tenth ribs on the right side posteriorly was resected and a catheter was introduced. Pleural irrigation with Dakin's solution eventually succeeded in clearing up the empyema. The sputum became negative and the patient was discharged.

Case 6: J. F., male, age 52, was admitted with a history of cough, expectoration, weakness and hemoptysis. Roentgenogram revealed infiltration of both tops with cavitation in the right infraclavicular area. The sputum was positive for tubercle bacilli.

Because of continued hemoptysis, pneumothorax was attempted on the right side.

During this procedure, after the injection of 150 cc. of air, the patient went into severe collapse, became cyanotic, pulseless and respiration was markedly diminished. The left arm and leg became rigid and the pupils widely dilated. Coramine was immediately given with pulse and respiration returning to almost normal rate. Blood pressure was 100/70. No air bubbles could be made out in the retinal vessels.

An hour later the patient's condition became worse; he went into a convulsion, then coma, and expired the next day. Autopsy permit was refused.

Case 7: R. G., female, age 21, was admitted with a history of cough, expectoration, weakness and loss of weight. The sputum was positive for tubercle bacilli. Roentgenogram revealed infiltration with cavitation in the right upper lobe.

Right pneumothorax was advised and an initial injection of 300 cc. of air was given. Two days later, during the second treatment and after the injection of 25 cc. of air, the patient went into collapse. She became rigid, very dyspneic and cyanotic. The pulse was weak and rapid. The pupils were somewhat dilated. The blood pressure was 80/40. Coramine was immediately given and the patient responded well. No air bubbles could be seen in the retinal vessels. Within twelve hours she had made a complete recovery.

The patient was discharged seventeen months later.

Case 8: H.L., male, age 35, was admitted with a history of cough, expectoration, hemoptysis and loss of weight. The sputum was positive for tubercle bacilli. Roentgenogram revealed infiltration in both upper lobes with cavitation in the right top.

Right pneumothorax was advised and during the initial treatment, after the injection of 100 cc. of air, the patient went into collapse. He became very dyspneic, cyanotic and the pulse was very weak. The pupils were slightly dilated and the eyes rotated to the left. Coramine was immediately given and within twenty-four hours the patient had made a complete recovery. No air bubbles could be seen in the retinal vessels. Four months later, because of progression of his pulmonary disease, the patient died.

Autopsy revealed bilateral disease with cavitation in the right upper lobe, tuberculous tracheitis and bronchitis, amyloid spleen and liver. No pathological changes were found in the brain.

Case 9: J. K., male, age 20, was admitted with a history of cough, weakness, streaking and loss of weight. The sputum was positive for tubercle bacilli. Roentgenogram revealed infiltration and cavitation in the left upper lobe.

Left pneumothorax was advised and, during the initial attempt, after the injection of 50 cc. of air, the patient went into collapse. He became cyanotic, pulse disappeared, respiration became feeble and the pupils widely dilated. Adrenaline was given and the pulse returned shortly, but the patient remained comatose for about three hours. The blood pressure was 80/50. He complained of severe headaches and blurring of vision for about six hours. Air bubbles could not be detected in the retinal vessels. Within twenty-four hours the patient made a complete recovery. Six months later the patient underwent a two-stage left-sided thoracoplasty with an excellent result.

Case 10: M. H., female, age 34, was admitted from another hospital with a history of cough, hemoptysis, loss of weight and dyspnea. The sputum was positive for tubercle bacilli. Roentgenogram revealed the presence of fluid in the left chest and infiltration with a small cavity in the right upper lobe. Thoracocentesis of the left chest showed the presence of an empyema. About 200 cc. of pus were removed from the left chest and

replaced by 150 cc. of 5 per cent gomenol and 100 cc. of air. This procedure was carried out every three weeks.

On the tenth treatment, following completion of the operation, the patient said that she was going to faint, tried to get up from the table and slumped into a coma. The patient became rigid, dyspneic and pulseless. Coramine was immediately given. The pulse and respirations came back and the patient's color improved. The pupils were widely dilated. The blood pressure was 80/60. Ophthalmoscopic examination showed presence of air bubbles in the retinal vessels. The patient was unable to see for two days and her vision was blurred for about a week. She made a complete recovery from the cerebral accident and went home against advice.

Case 11: M. B. (case of J. B. A.), male, age 42, was admitted with a history of cough, expectoration, weakness and loss of weight. The sputum was positive for tubercle bacilli. Roentgenogram revealed infiltration and cavitation in the right upper lobe.

Right pneumothorax was advised and on the initial treatment the patient received 200 cc. with good readings. Two days later, while the patient was receiving his second treatment and after the injection of 50 cc. of air, he complained of sudden pains in the head, became dyspneic, pulseless, rigid and cyanotic. Adrenaline was immediately given and the pulse returned. His pupils were widely dilated and ophthalmoscopic examination showed the presence of air bubbles in the retinal vessels. The patient complained of blurring vision and terrific headaches. The blood pressure was 94/50. About half an hour later the patient had a convulsion, became slightly irrational and developed a left-sided hemiplegia with aphasia. On the next day the patient complained of inability to move the left arm and leg. That afternoon the patient had another convulsion involving the right arm and leg but with no ensuing hemiplegia. By the fourth day the patient had made a complete recovery although he still had some aphasia.

Six months following the cerebral embolism, because of progression in his pulmonary disease, the patient died.

Case 12: M. S., female, age 26, was admitted with a history of cough, expectoration, night-sweats and loss of weight. The sputum was positive for tubercle bacilli. Roentgenogram revealed bilateral infiltration with cavitation in the left upper lobe.

Left pneumothorax was advised. During the injection of 2 cc. of a 1 per cent solution of novocaine in the seventh intercostal space on the left side in the posterior-axillary line preparatory to pneumothorax, the patient suddenly went into collapse, appeared prostrated, developed generalized clonic convulsive movements, loss of consciousness, cyanosis, feeble breathing and became pulseless. Coramine was immediately given both by subcutaneous and intravenous routes but the patient died within two minutes.

A postmortem examination was performed two hours after death, and revealed bilateral pulmonary fibrocaceous tuberculosis with cavitation in the left upper lobe; bilateral obliterative pleuritis; puncture wound of the left pleural cavity; examination of the brain was negative.

Microscopy revealed no cause of immediate death. The medical examiner concluded that this was a true case of novocaine poisoning.

SUMMARY

1. A brief review of the literature on pleural shock and cerebral embolism has been presented.

2. Experimental evidence and clinical observations definitely support the theory of cerebral embolism.

3. The symptom-complex of cerebral embolism is characterized by pallor, dizziness, ocular disturbance, tonic and clonic convulsions, unconsciousness, changes in the respiration and circulation, paralysis and, sometimes, death.

4. The treatment consists of lowering the patient's head and giving cardiac stimulants.

5. The prognosis in cerebral embolism depends upon the amount of air entering the blood-stream and the region of the brain most seriously involved.

6. At the Boston Sanatorium in a series of 90,120 pleural punctures, we have encountered 12 cases with 3 fatalities. One of the fatal cases we have attributed to novocaine poisoning.

7. There are two types of serious reactions following novocaine poisoning.

8. Novocaine in a 1 per cent solution should be employed only for the initial pneumothorax treatment and not for the subsequent refills.

SUMARIO

1. Preséntase en este trabajo un breve repaso de la literatura relativa al choque pleural y a la embolia cerebral.

2. Los datos experimentales y las observaciones clínicas apoyan decididamente la teoría de la embolia cerebral.

3. El complejo sintomático de la embolia cerebral caracterízase por: palidez, vértigo, trastornos oculares, convulsiones tónicas y clónicas, pérdida del conocimiento, alteraciones respiratorias y circulatorias, parálisis y a veces la muerte.

4. El tratamiento consiste en bajar la cabeza del enfermo y administrarle tónicos cardíacos.

5. En la embolia cerebral el pronóstico depende de la cantidad de aire que penetre en el torrente sanguíneo y en la región cerebral más afectada.

6. En el Sanatorio de Boston en una serie de 90,120 punciones pleurales, se han observado 12 casos de embolia cerebral con tres muertes. Uno de los casos letales se imputó a envenenamiento por novocaína.

7. Hay dos clases de reacciones graves consecutivas al envenenamiento por novocaína.

8. La novocaína al 1 por ciento debe emplearse únicamente para el neumotórax terapéutico inicial y no para los rellenos subsiguientes.

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FAMILY HISTORIES IN TUBERCULOSIS¹

S. E. SIMPSON

One of the most interesting and profitable methods of discovering new cases is by means of contact examinations. This requires an intimate study of the home environment and personal knowledge of the family personnel and problems. An investigation of the home and examination of all contacts requires both time and patience because many individuals have to be educated and shown the necessity for submitting to an X-ray examination of the chest. The greatest difficulty lies not with the younger but the older generations, the latter being reluctant in a great many instances to make the necessary effort to attend a clinic held at the sanatorium.

Many physicians, surprisingly enough, and the majority of the lay people still cling to the old idea of heredity as playing an important part in the spread of tuberculosis in any one family. One reason for this misconception is the method of taking histories where emphasis is placed on obtaining all the names of persons in the family and the causes of death in past generations. Also, all know of entire families wiped out by tuberculosis in the old days without realizing the fact that the disease was not limited to the family but undoubtedly spread outside the family circle at the same time. In attempting to correct this attitude, a series of five family charts have been used to illustrate the extent of tuberculosis both within and without the family. These begin with family tuberculosis in its simplest form proceeding gradually to its most complex form where it was a community rather than family problem, emphasizing the public health importance of disease. Statistics were avoided as the audience immediately loses interest and cannot remember figures. However, the family charts convey a visual image of the path of infection from one individual to another, from one family to another through contact.

The value of this method of finding new cases has been proved many times by many authors and is generally accepted by all. Opie and McPhedran (1) demonstrated in a series of articles that over 9 per cent of household contacts developed tuberculosis when exposed to positive sputum cases and that 6 per cent developed the disease when living with negative sputum patients. Beeuwkes, Hahn and Putnam (2) verified these conclusions in a statistical review of their work in the field. Edwards (3), in an excellent article on *Case Finding in Tuberculosis, an Adult Problem*, concludes that "After a careful perusal of the volume of material in current literature on tuberculosis surveys, it becomes immediately obvious that the great bulk of our effort in the past has been devoted to contact examinations. This is fundamental in any tuberculosis program. The problem among this group that is presented time and again is that as a rule we only examine about one-half of the known contacts and that the percentage is highest among the younger ages where we do not expect to find manifest tuberculosis.

¹ From the Jefferson County Sanatorium, Watertown, New York.

The adult ages are the most important and demand greater effort to secure coöperation."

The importance of carrying the investigation outside the household is emphasized in a paper by Downes (4) who concludes, in an interesting study of families with tuberculosis in Cattaraugus County, New York, that "the spread of serious disease from tuberculous families into the larger universe, the community, is at least as great as within the family."

Our study of tuberculous families includes both points brought out by the last two authors. Every person, irrespective of age or sex, with special emphasis on the older age groups, was asked to come in for examination, with very satisfactory results as to coöperation. All possible contacts outside the family likewise were requested to submit to an X-ray examination. In many cases these contacts presented themselves voluntarily before being interviewed by the investigating nurse. In the last group to be discussed, where many persons in a small village had tuberculosis, an attempt, partially successful, was made to examine all the inhabitants by means of a mass survey conducted through the assistance of the local Grange Society.

The examination consisted of a history, both family and personal, a physical examination when indicated by suspicious or manifest disease, a fluoroscopic and roentgenographic examination and a Mantoux tuberculin test on those under 20. The coöperation of the family physician was first obtained by getting his permission to enter the home for investigation and by sending complete reports of the clinic examination to him. Likewise, the results of the survey are discussed with the heads of the family so that they are entirely familiar with the purposes and results of the work accomplished.

The family histories are divided into five groups starting with the simplest picture where tuberculosis involves one person in each of three succeeding generations. The second group reviews the findings in a larger family of 28 members with tuberculosis limited as far as we know to the family circle. The third group presents a slightly more complicated picture in that two families are involved with a definite history of contact between the two. The fourth group carries this one step further in that a number of persons with tuberculosis are related only through contact, each with a succeeding one, until we have 8 cases, only 2 of whom are blood relations, a father and his baby son. The last presents the most complex problem, as nine families had to be included, five of them related by marriage and four only by contact with some member of the first five. Here the path of infection appears to be quite clear, however, and illustrates the wide-spread nature of the disease and dissemination of the tubercle bacillus.

This first family shows the path of infection in its simplest form, involving three generations: maternal grandmother, mother and daughter. The disease has been apparently limited to immediate members of the family, as no other case of tuberculosis has been traced back to it.

GROUP I

Case 1: A 23 year old married woman was first admitted to the clinic on March 17, 1938 for a chronic, productive cough, night sweats, loss of appetite and weight for several

months. Her chest film showed bilateral infiltration with cavity formation and she was immediately hospitalized and collapse therapy started on one side. However, she left against advice, as neighbors reported suspected infidelity on the part of the husband. Later, she developed an empyema, resulting in a broncho-pleuro-cutaneous fistula, in 1941. She is still living but in poor health.

Case 2: Six days later, March 23, 1938, her only child, a girl of 2, was admitted as a patient with a diagnosis of tuberculosis of the left knee. The family physician had treated her for rheumatic fever with involvement of the knee joint. Her tuberculin (Mantoux) reaction was positive. A chest film showed infiltration at the right base and of the hilar nodes. The knee was markedly swollen and a film revealed destruction of the joint surfaces. After a fusion operation she was discharged well in 1941. Unfortunately, the mother insisted that she live with her and nothing could be done to prevent this.

The father, aged 28, was examined in 1938 and at yearly intervals until 1942, when he joined the armed forces and no evidence of tuberculosis was ever found.

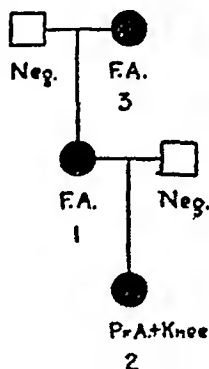


CHART 1. Group I. Square: male; Circle: female; Neg.: no tuberculosis; F. A.: far advanced; Pr. A.: primary, active; Knee: tuberculosis of knee joint.

Path of infection: grandmother (case 3) to mother (case 1) to daughter (case 2).

Case 3: On January 10, 1940, the 45 year old maternal grandmother visited this child during a severe snowstorm. She collapsed at the door and the assistant physician persuaded her to have an X-ray film of the chest for possible heart disease as she had refused examination during the previous two years. She was found to have far advanced pulmonary disease with bilateral infiltration and large cavity formation. She refused to accept sanatorium care and died at home ten months later. Her husband would only consent to a fluoroscopic examination and no pulmonary disease was seen.

Summary: The story is simple, the tuberculosis passing from grandmother to the mother and finally daughter. The first patient is dead, the second critically ill and the third well. The male members were not involved (see chart 1).

GROUP II

The history of tuberculosis in this next family covers a period of eighteen years with one member still under active treatment. The source was never found but the disease has apparently been limited to the family. Of the 22 persons involved, 14 show infection either by positive Mantoux reactions or active tuberculosis.

found in the sputum. After two years of curing she was discharged arrested and in 1939 was called apparently cured.

Her oldest daughter, 8 years, had a positive Mantoux test on the first examination but no pulmonary involvement. The second oldest, 6 years, also had a positive Mantoux reaction and active primary pulmonary disease. This one developed active tuberculous cervical adenitis which was treated successfully by surgery. Her only son, 4, had a positive skin reaction and healed primary tuberculosis of the lungs.

Case 5: About one month later, November 11, 1930, the 8 year old son of the first patient, who died of tuberculosis in 1927, was admitted with an active primary lesion in the right upper lobe. His Mantoux test was positive. He was discharged in 1935 as having healed primary tuberculosis. Following an hemoptysis he returned to the sanatorium with definite infiltration in the same area as the primary lesion was located. Artificial pneumothorax was started with a satisfactory collapse, but within a year the tuberculous disease had involved the left upper lobe and collapse therapy was started on that side. He finally left against advice in August, 1944 with bilateral pneumothorax. Only once during the ten years in the sanatorium did we find tubercle bacilli in the sputum, and that was in June, 1944, shortly after a recent spread of the disease. He is still under treatment in the clinic.

Case 6: On December 30, 1930, the third oldest sister in this family was examined as a contact, at the age of 23, and was found to have tuberculous infiltration in the right upper lobe. She had no pulmonary symptoms and refused to enter the sanatorium. However, four years later, July 2, 1934, she came in following several moderately severe hemoptyses and remained only about four months, leaving against advice. No sputum was obtained for examination. Reexamination in 1938 and 1941 showed the disease to be apparently cured.

She had one illegitimate son who had a positive Mantoux reaction and a calcified node in the right lung when first examined one month previous to his mother's first examination. He is alive and well at the present time with a healed primary pulmonary infection. The mother was married in 1937 and her husband, when examined shortly afterward, was negative for tuberculosis.

Two remaining sisters came to the clinic in 1929 and 1930 and no evidence of tuberculosis was found. Three young brothers in this large family were checked in 1930. Two had healed primary lesions and one had only a positive skin reaction. The fourth brother and last member was examined in 1934 and had a healed primary lesion with positive Mantoux reaction at that time. None has returned for reexamination.

The parents were checked in 1932 and 1934 and no evidence of tuberculosis was found by X-ray examination.

Summary: A large family of 10 children and 6 grandchildren were investigated between 1926 and 1930 because of contact with the oldest sister who died of tuberculosis in 1927, one year after the diagnosis was established. The fifth sister died of the same disease in 1929 and 2 others, the second and third, were treated in the sanatorium for active lesions in 1932 and 1934, respectively. Two sisters and the parents were negative but the 4 young brothers had all been infected as evidenced by positive tuberculin reactions and in 3 by healed primary lesions in the lungs.

Two of the grandchildren have active tuberculosis. The only son of the first patient has been in the sanatorium for five years on two separate occasions, a total of ten years, the latter time with moderately advanced tuberculosis. The second grandchild, the daughter of the second sister, was admitted for tuberculosis of the spine, treated for six years and then developed bilateral tuberculous nephritis from which she is still an invalid. One of her sisters had a tuberculous cervical adenitis, treated surgically by a local surgeon and not in the sanatorium.

No one knows how the tuberculosis entered the family as the clinics were just under way when the first case was discovered and no contact work was being done at that time, in 1926. Of the 28 persons, 2 have died, 2 have active disease at the present time, 2 more have apparently healed lesions in the lungs, 6 have healed primary lesions in the lungs and 2 more have positive Mantoux reactions without involvement of the lungs. The parents and 2 sisters are the only ones without infection, based on X-ray examinations alone. Three husbands are also negative (see chart 2).

GROUP III

This group represents the involvement of two families, unrelated except through contact of one individual in the first with another individual in the second. The tuberculosis has broken out of the limits of the household to invade another.

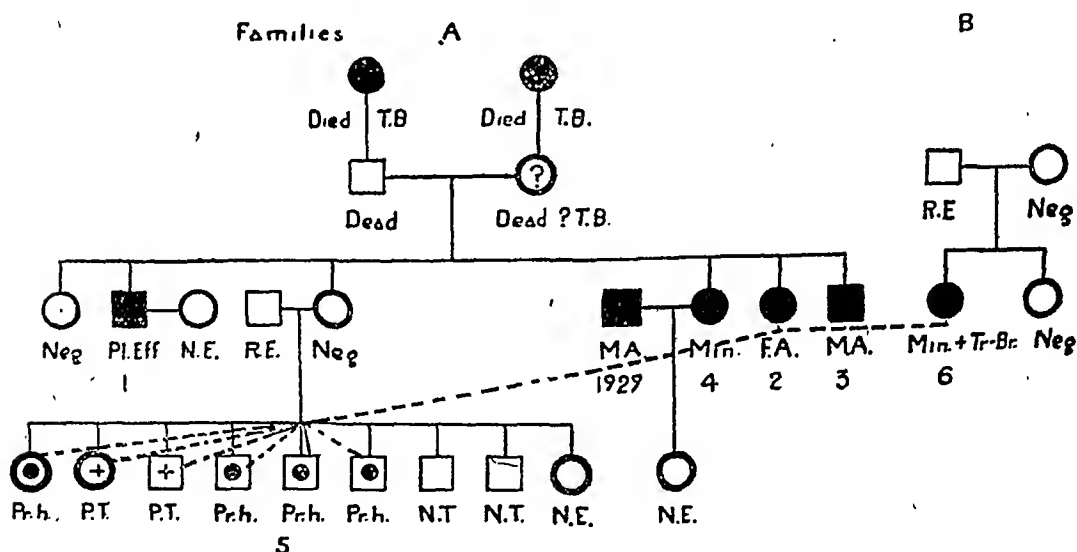


CHART 3. Group III. Square: male; Circle: female; Neg.: no tuberculosis; R. E.: refused to be examined; N. E.: not examined; F. A.: far advanced; M. A.: moderately advanced; Min.: minimal; Pl. Eff.: tuberculous pleural effusion; Tr.-Br.: tracheobronchial tuberculosis; Pr. H.: primary, healed; P. T.: positive intracutaneous tuberculin; N. T.: negative intracutaneous tuberculin.

Path of infection: Family A, 2 great-grandmothers to (probably) grandmother to 4 children (cases 1, 2, 3 and 4). From case 4 to 6 out of 9 nieces and nephews (case 5) and to companion (case 6) in Family B.

Case 1: (Family A) A 40 year old married man was referred to the clinic by his family physician on April 9, 1934 for a left pleural effusion; 500 cc. of clear fluid was aspirated one month later and the patient never returned for another examination. The diagnosis was tuberculous pleural effusion. He is living and well to-day. His wife was never examined. No contact examinations were done.

Case 2: (Family A) On November 23, 1936 his 25 year old single sister was admitted to the sanatorium with a diagnosis of far advanced pulmonary tuberculosis. She was a school teacher and had had a productive cough with loss of appetite and weight for at least one year previous to admission. She had been treated for bronchitis. Bilateral pneumothorax was tried but she died on February 15, 1937.

A careful family history was obtained from her and other members of the family. Her grandmothers had both died of tuberculosis many years previously and she had had no contact with them. Her father had died of "cardiac disease" several years ago. Her mother also was supposed to have died of "cardiac disease" but she had coughed and raised sputum for a number of years before her death, so there is a strong possibility that she had tuberculosis, especially in view of the fact that her mother had died of the disease.

Case 3: (Family A) The 23 year old brother (the youngest of this family of 6 children) came from another state to attend his sister's funeral and was persuaded to submit to an examination on February 18, 1937. He had not had any pulmonary symptoms but his chest film revealed tuberculous infiltration in the left upper lobe with a small cavity. Sputum was obtained and this was positive for tubercle bacilli. He was admitted one month later, remaining in the sanatorium for nine months, being discharged with artificial pneumothorax collapse of the involved lung. Later he developed an effusion and empyema in another city, but made a good recovery.

Case 4: (Family A) The day following the admission of her 25 year old sister, another member, aged 32 and single, was examined and found to have a minimal tuberculosis, probably inactive. She was followed in the clinic for seven years and finally classified as apparently cured. She married a former patient and had one child whom she has refused to have X-rayed or tuberculin tested.

Case 5: (Family A) Under this number, 8 children are included, all being sons and daughters of the second oldest sister of this family. The mother, aged 40, was examined along with her children on March 30, 1937, because of contact with the 25 year old school teacher, her youngest sister. No evidence of tuberculosis was found in her X-ray film. Her husband refused to be examined. All the children, from the ages of 2 to 18 years, were X-rayed and tuberculin tested. The 6 oldest all had positive reactions and 4 showed healed primary lesions. The two youngest, 2 and 4 years, respectively, were negative both then and five years later.

The explanation of this difference in tuberculin reactions between the 6 oldest and 2 youngest lies in the fact that these 6 had spent their summer vacations with their aunt who died of tuberculosis, while the 2 youngest had been kept at home by the mother so did not come in contact with an active case. Thereby, they escaped infection.

Case 6: (Family B) Almost one year after the admission of case 2, another school teacher, 29 years old and single, was admitted as a patient on July 26, 1938, for minimal tuberculosis with a positive sputum. She had been X-rayed five years previously and no evi-

dence of tuberculosis was found. While in college she had a tuberculin test done in 1934 and this was negative. During the next three summer months she attended summer school and was a roommate of case 2 in Family A. After four months of bed-rest without improvement collapse therapy was tried, also unsuccessfully, as the sputum remained positive. She was transferred to another sanatorium for pneumonolysis and it was discovered that she had severe tracheobronchial tuberculosis. She died fourteen months after her admission to our sanatorium.

Her father refused to be examined but her mother consented and no tuberculosis was found by X-ray examination. Her younger sister was finally examined in 1944, having refused to be X-rayed up to that time, and no tuberculosis was found.

Summary: Two grandmothers in Family A died of tuberculosis many years ago. The mother was supposed to have died of "heart disease" at 60 but had very suspicious pulmonary symptoms for several years before her death. There were 4 sisters and 2 brothers in the family. Two of the sisters were found to have pulmonary tuberculosis, the youngest dying of this disease in 1937. The other 2 had no pulmonary disease. Both brothers had tuberculosis, the older a tuberculous pleural effusion, diagnosed in 1934 and the younger moderately advanced disease, in 1937. The second sister had 8 children and the 6 oldest had positive Mantoux reactions, 4 of them showing primary healed lesions by X-ray examination. All had been exposed to the youngest aunt with far advanced disease. The 2 youngest escaped, as they were not exposed, being considered too young to spend vacations with the aunt.

Finally, this 25 year old aunt infected her college roommate who died of tuberculosis two and one-half years later. No other member of this second family has been involved. The history of exposure of this patient in Family B is quite clear (see chart 3).

GROUP IV

This next group of cases indicates the spreading nature of the infection irrespective of blood relationship. The first 3 cases were found as a result of clinic examinations but the remaining group as discovered through contact work by the nursing staff.

Case 1: A 57 year old, married man, of Roumanian birth, was referred to the clinic by his family physician on May 24, 1932, for a persistent productive cough and loss in weight of one year's duration. A diagnosis of far advanced tuberculosis was made on X-ray and sputum examinations and he was admitted to the sanatorium where he died three months later. His family lived in Roumania.

Case 2: A second Roumanian man, also married and 40 years old, was examined on July 26, 1932 with similar symptoms as the first. He also had far advanced tuberculosis and died in the sanatorium nearly four years later. His wife had died in childbirth. He had 4 children all of whom had positive tuberculin reactions, 3 accompanied by healed primary pulmonary lesions. This patient was a close friend of the first patient.

Case 3: The third Roumanian man, aged 55, was admitted to the sanatorium on September 1, 1938, with far advanced pulmonary tuberculosis and positive sputum. He died twenty-two months later. His wife, a sister to the wife of the first patient, lived in Rou-

mania with her daughter. At the time of his admission he was boarding with a fourth Roumanian, his wife and their second oldest son. This family was examined immediately, resulting in the discovery of a series of new cases during the next five years.

Case 4: The second son of the above family was examined five days after case 3 was diagnosed. He admitted that he had been losing weight and had had a productive cough for several months. The X-ray film showed a unilateral lesion with small cavity formation. The sputum was positive; he was admitted to the sanatorium where he remained for about one year. Films taken in 1943 revealed infiltration in the opposite lung but he refused to be readmitted. At the time of his admission he was 24 and married to a 19 year old girl who is the next case.

Case 5: At the time of her husband's admission to the sanatorium this young woman was a maid in the infant's ward in a local hospital. She was discharged immediately but did not come in for examination until November 1, 1938, at which time her X-ray film showed

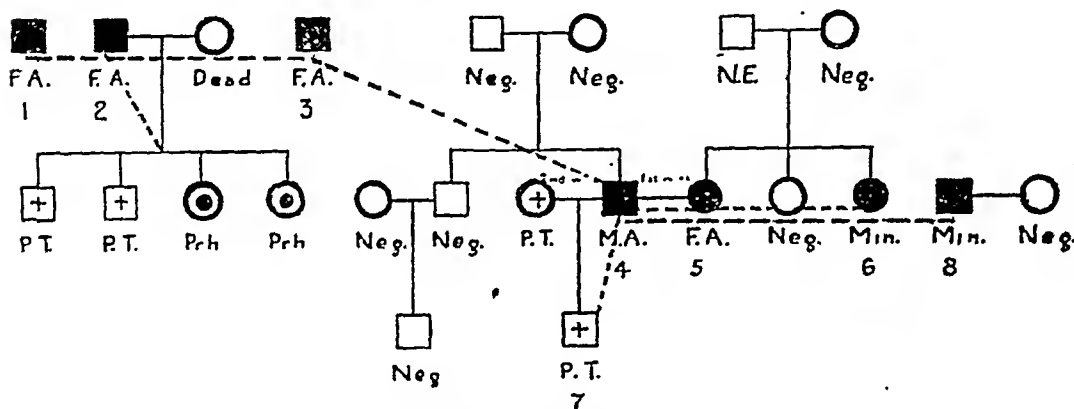


CHART 4. Group IV. Square: male; Circle: female; Neg.: no tuberculosis; N. E.: not examined; F. A.: far advanced; M. A.: moderately advanced; Min.: minimal; Pr. H.: primary, healed; P. T.: positive intracutaneous tuberculin.

Path of infection: Cases 1, 2 and 3 probably infected each other. Case 3 infected case 4 who in turn infected his wife (case 5) his son (case 7) and friend (case 8). Wife (case 5) probable source for sister (case 6). Case 2 infected his 4 children.

infiltration and cavity formation in one lung. Collapse therapy was tried and was unsuccessful. She left against advice after a few months' treatment. The disease continued to progress but she remained extremely uncoöperative, dying supposedly of "heart disease" in 1944 in another state. She had divorced her husband in 1940 and had been remarried to a soldier.

Case 6: This wife had 2 sisters, the older refusing to be examined but the second, aged 15, came in on May 28, 1938 and had a positive tuberculin reaction but no evidence of pulmonary disease. Four years later, on reëxamination, an early infiltration was found in the left lung and she was admitted but remained only three months, leaving against advice. On June 21, 1943, the disease had become far advanced and she was having severe hemoptyses. She was readmitted and made a successful recovery.

Her mother was X-rayed several times and never showed any evidence of tuberculosis. The second sister was fluoroscoped by her family physician, as she refused to come to the sanatorium, and he reported that her lungs were clear.

Case 7: The 24 year old son who had tuberculosis and had divorced his first wife married again in 1942. On August 26, 1943, their 5 months old son was brought in by the mother and his tuberculin test (Mantoux) was positive but the chest film was negative. While no evidence of active pulmonary disease has been found in this baby he should be included in this series of cases.

Case 8: A 43 year old married man was rejected for army service in August, 1943 for pulmonary disease and came to the clinic for examination. A small area of infiltration was found in the right upper lobe which was diagnosed as minimal tuberculosis. He has refused to return for further X-ray examination. He was a close companion of the 24 year old son (case 4) and in all probability contracted the disease from him.

Summary: It is impossible to state whether the first 3 cases, all Roumanian men, infected each other, starting with one of the first 2, or whether there were 3 separate sources. However, the third man, diagnosed in 1938, was the source, direct and indirect for the remaining 5 cases. He first infected the younger of 2 sons, who infected his wife. She, in turn, was the source for the youngest sister. After divorcing his first wife, he remarried and infected his 5 months old baby in 1943. He also was probably the source of infection for the 43 year old man rejected for the army service in 1943.

By the end of 1944, 4 of the 8 patients had died of tuberculosis, 2 still had active pulmonary disease, one remains uncoöperative and refuses reëxamination and the baby is still living and well (see chart 4).

GROUP V

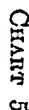
This last group of cases presents a very complicated picture but illustrates quite clearly the path of the tubercle bacillus through nine families, five of whom are related by marriage. The descriptions of the cases are limited to those with active disease and are numbered according to the date of their discovery.

The families are alphabetically numbered from A to J, with families A through E being related directly or indirectly by marriage. The whole trouble started in Family A with the maternal grandmother who died of tuberculosis in 1907, and new cases were still being found nearly thirty-seven years later.

Case 1: (Family A) The first case to be diagnosed was a man of 55 who came to the clinic on September 26, 1929, complaining of a chronic cough with sputum of about three years' duration. The X-ray film showed bilateral tuberculosis with cavity formation. The sputum was positive for tubercle bacilli. His mother had died of tuberculosis in 1907 at the age of 60. A brother-in-law also had died of the same disease, in the same house and bed, in 1918. He himself, had been the welfare officer, noted for his hard nature in handling welfare cases, and when retired conducted a commercial flower garden in the small village of about 200 population.

He refused sanatorium care until 1939 and, then, stayed only a few weeks, leaving against advice as he could not hear anyone, being very deaf. He became progressively worse, developing asthmatic symptoms and died in 1943, at 69, in the same bed in which his mother and brother-in-law had died.

Case 2: (Family A) His third oldest son was examined in 1930 at the clinic, also complaining of cough and expectoration of several years' duration. He was 24 and married



Diab.: diabetes; Neph.: chronic nephritis.

Path of infection: Great-grandmother, Family A, to son (case 1) and son-in-law. Son (case 1) to his son (case 2) to wife (case 3) and 3 children. Case 1 also to at least 2 in Family D (cases 8 and 9) and one child in each of four other families F, G, H and J (cases 4, 5, 6 and 7). In turn, case 8 probable source for 3 children, 2 with active primary lesions (cases 10 and 11), his wife and her two sisters, positive tuberculins, and finally his mother (case 12).

but had no children at that time. The X-ray film revealed a unilateral infiltration with cavity formation and his sputum was positive. He refused to enter the sanatorium but consented to be examined at intervals. The last X-ray film showed slowly progressive disease, in 1944, with at least one cavity. He spends his summer months working on farms and is uncoöperative. His two brothers lived in another county and could not be examined.

Case 3: (Family A + B) The 18 year old wife of the above patient was examined in 1930 and found to have a suspicious lesion in one apex, which later was diagnosed as minimal, apparently cured. She never had any pulmonary symptoms. By 1938, they had 3 sons, from 5 months to 7 years old. The oldest had a positive Mantoux test with a healed primary lesion. One year later the second son had a positive Mantoux and negative X-ray film, and the youngest developed his positive Mantoux test in 1942 with X-ray evidence of a healed primary lesion.

Case 4: (Family H) On May 14, 1940 a boy of 16 was admitted to the sanatorium with a diagnosis of minimal pulmonary tuberculosis and pleural effusion. He had been X-rayed in 1932 because of a positive Mantoux reaction and an enlarged calcified node was noted in the left hilum. The next X-ray film was taken seven days before admission, showing the effusion. He remained in the sanatorium for nine months and was discharged well. Two years later, the clinic nurse discovered that he had been working for one or more summers in the garden of case 1, previous to his admission. Also his family lived in the same small village and came in close contact with members of Family A, which included cases 1, 2 and 3. Three out of the 4 sisters had positive tuberculin reactions, with 2 showing healed primary lesions by X-ray examination. The parents were negative by X-ray examination.

Case 5: (Family G) Three months later, on August 9, 1940, a 16 year old girl, also living with her family in the same village, was admitted with a diagnosis of left pleural effusion and positive Mantoux test. She had been ill for a short period of time. After ten months as a patient, she was discharged well but two years later her X-ray film showed a suspicious area of infiltration in the left upper lobe. In checking over her history for possible contacts it was found that she had worked in the garden of case 1 for at least one summer and the whole family lived on the same street as Family A. Her 2 sisters and one brother all had positive Mantoux tests. The parents had no evidence of adult-type pulmonary tuberculosis.

Case 6: (Family F) Three weeks after case 5 was admitted, a young man of 21 years was transferred from a local hospital with a diagnosis of tuberculous peritonitis, discovered at operation for possible appendicitis. His chest film revealed tuberculous infiltration in the left upper lobe with an effusion at the base. He was discharged as arrested nine months later. In looking for a source of infection, it was found that he too had been hired by case 1, the gardener, for several months each summer. His family did not live in the village and did not come in contact with Family A. His parents were negative but 2 sisters and 2 brothers, younger than the patient, all had positive Mantoux tests, and 2 brothers were negative. He, later, was inducted into the Army and was killed on Invasion Day in 1944.

Case 7: (Family J) A 13 year old boy was diagnosed as having a pleural effusion on November 6, 1941, and admitted to the sanatorium where he remained only twelve days,

his grandfather taking him out against advice. Again, the only known contact was with Family A, where he had resided next to them in the same village. The rest of the family lived in another state and he lived with his grandparents who refused examination. The boy cleared up the effusion within a year and is now well.

Case 8: (Family D) A 22 year old, married man came to the clinic on June 2, 1942, because of loss of weight, cough with expectoration and hoarseness of one year's duration. The X-ray film of his chest showed bilateral tuberculosis with large cavity formation. The laryngeal examination revealed ulceration and induration of both cords, the arytenoids and epiglottis. The sputum was positive for tubercle bacilli. Although the prognosis was bad, he was offered collapse therapy in an attempt to arrest the progress of the disease but left against advice and died seven months after discharge, or nine months after the case was diagnosed.

When investigating the case for contact, it was discovered that he, too, had worked in the garden of case 1 for several summers, and that his family had lived in the same village, in fact were close neighbors of Family A for three or four years. At the time of his admission, the other members of the large family were examined. The parents were both negative. His maternal grandfather had a calcified primary lesion. The grandfather had been married three times, the first wife died of tuberculosis in 1898, the second (the grandmother of this boy) of nephritis, and the third, 65 years old, was living and well. The oldest sister, case 9, had minimal tuberculosis, the second sister was stated to have a minimal lesion but she lived with her husband in another state, one brother and his wife had positive tuberculin tests and 3 other brothers were negative. The patient's wife and her 2 sisters had positive Mantoux tests but negative films. Their parents were negative according to X-ray examination.

Case 9: (Family C) This patient was the oldest sister of case 8, and was examined shortly after his diagnosis was established. She had been examined in school in 1936 at the age of 17 and no evidence of tuberculosis was found, but six years later, June 3, 1942, there was definite infiltration in the right upper lobe. On reexamination one year later there was no change. She has been very uncoöperative since then, refusing to be X-rayed again.

Her husband had a healed primary lesion which had been diagnosed in 1928 during a school examination when he was 18. There were 3 daughters. The oldest, 4, and the youngest, 15 months, had negative tuberculin and X-ray tests but the middle one is the next case.

Case 10: (Family C + D) This was a girl of 3, the second of 3 daughters of case 9. Her tuberculin test was positive and her X-ray film, taken on July 18, 1942, six weeks later than her uncle's, case 8, showed a diffuse infiltrative area extending from the left hilar region. The diagnosis was primary pulmonary tuberculosis, active. The mother has refused to bring her back for further examinations and refused to have her admitted for treatment in the sanatorium. Her contact was the 22 year old uncle, brother to her mother, who died in 1943. The 2 families lived near each other and he was very fond of this niece. There is a possibility that the mother infected her but no sputum was ever obtained from the mother for examination.

Case 11: (Family B + C) A cousin of case 10, aged 11 months, was examined on July 2, 1942, because of contact with case 8, although no relation to him. This boy had a lesion identical with that of the previous patient and was diagnosed the same. He has

been followed in the clinic for the past two years and calcification has appeared in the area of infiltration. His health has always been excellent.

His father was the brother of the father of case 10, and he had a healed primary lesion. His mother was a sister of case 3 with minimal tuberculosis, whose husband had moderately advanced disease (case 2). His maternal great-grandmother, who died of tuberculosis in 1898, was the first of 3 wives of the maternal grandfather of the 22 year old man (case 8).

Case 12: (Family D) In July, 1944 the 46 year old mother of the 22 year old man (case 8) was reexamined and found to have bilateral infiltration with multiple cavity formation and positive sputum. She had been well when first X-rayed on June 3, 1942, after her son was found to have tuberculosis. One year later she apparently developed diabetes and shortly after that had a severe cold from which she never recovered. The only known contact was her son, although her oldest daughter (case 9) had minimal disease with questionable activity according to one examination.

Summary: In studying these cases there seem to be two centres of infection, the primary in Family A and secondary in Family D. The first history of tuberculosis occurred in a 60 year old woman who died of the disease in 1907. Her youngest son died of tuberculosis in 1943 at the age of 69, fourteen years after the diagnosis was established. Also one of her sons-in-law died of the same disease in 1918 in the same home.

Her son, in turn, was the source for a number of persons, as he conducted a commercial garden and hired young people to help him in the summer. He infected his youngest son (case 2), and at least 5 others (cases 4, 5, 6, 7 and 8), one girl and 4 boys, varying in age from 15 to 22. He may also have been the source for a sister of case 8, who had minimal disease and had lived near him.

The secondary centre starts with the 22 year old man (case 8), a contact with the 69 year old man, described in the preceding paragraph. Two children (cases 10 and 11), 3 years and 15 months of age, respectively, had active primary lesions identical in position in the lungs. One, the older, was a niece and the second was her cousin but no relation to the man. Another niece, 4 years old, and not included among the active cases, had a positive tuberculin reaction with calcified lymph nodes in one hilum. All these children frequented the home where he lived and were intimately exposed to tubercle bacilli. Likewise, his young wife and her 2 sisters were equally closely exposed, resulting in positive tuberculin reactions. Finally his mother (case 12) became ill about the time of his death and was diagnosed as having tuberculosis one year later, although she had a negative chest film two years previously.

Credit cannot be given to contact examinations for the discovery of a number of these cases, as the relationship was not revealed in several cases until one or more years had elapsed after their diagnosis was made. However, as the picture unfolded and the pattern became more distinct, active work among these families did uncover other active cases who, otherwise, would have remained unknown. The history of infection goes back to 1907 and the last patient was admitted in 1944 with no certainty that further cases will not appear in the future as many of these persons are very uncoöperative and are free to spread bacilli still further (see charts 5 and 6).

DISCUSSION

The case histories and charts of five families or groups of families are presented to emphasize the importance of contact examinations in the search both for the original and new cases of tuberculosis. They can be duplicated in any sanatorium clinic from its records and are especially useful in lectures to lay and medical organizations who generally have mistaken ideas about the importance of heredity in contrast to contact as the important factor in the further spread of the disease. The first two family charts tend to stress the "inherited tendency" but as the charts progress in complexity, involving more than one family, the contact factor becomes increasingly more important.

The greatest difficulty encountered in family contact work is not in getting the contacts to the clinic but rather in persuading the newly discovered cases to accept sanatorium care. In nearly every family one or more persons were absolutely opposed to entering the sanatorium either for treatment or isolation from the home. Also the long period of treatment necessary in many cases resulted in their discharge against advice as they got discouraged or some disturbing element in the home arose to interrupt their course. That parents would deliberately and knowingly expose their children to infection is past comprehension, yet it was encountered in several cases, especially in the last two groups of families.

The New York State Health laws are quite specific about the commitment of positive sputum cases who can be considered a menace to the health of the community. Its application in a large city is comparatively easy but it is a different story in small communities. Here the physician may be both family physician and part-time health officer, who is naturally reluctant to commit his own patients to a sanatorium for treatment against their own desires. He not only may antagonize the family but the entire community who often knows all the facts but misinterprets his good intentions. He would require the moral support of others in the town or village which is definitely lacking at the present time. This apathy to tuberculosis as a public health menace is in marked contrast to that encountered in the acute infectious diseases such as infantile paralysis, smallpox, etc.

Only intensive education of the public, such as can be carried on by means of family histories and charts, will arouse interest and sentiment in favor of stricter enforcement of the public health laws concerning this disease. In addition, these histories, illustrating cases in their own county and township, stress the importance of X-ray examination of all contacts of a positive-sputum case, both inside and outside the household, and of the wide-spread nature of the disease. They also tend to counteract the fatalistic attitude of the public toward tuberculosis, on the basis of the mistaken idea that it is an inherited disease and a uniformly fatal one.

SUMMARY

Five families or groups of families have been presented as a study in the spread of tuberculosis, both inside and outside the immediate household. The path

of infection from one person to the next has been traced as accurately as possible, from the clinic records. In each group the percentage of contact examinations is high with very few persons refusing to cooperate.

The first family traces the disease from the grandmother to her daughter and granddaughter, with no cases outside.

The second family reveals the infection of 8 out of 10 children and all of the grandchildren, resulting in 2 deaths and 4 other cases who have required sanatorium care during a period of eighteen years. The source of the infection was never found, as the first case was discovered in 1926 before intensive contact examinations were started.

The third group includes two families, the youngest sister in the first being the source for the disease found one year later in a sister in the second. Both of these patients are dead and 2 other patients had active tuberculosis when first examined. The original cases were the 2 grandmothers and possibly the mother, all of whom are dead.

The fourth group includes a series of cases of tuberculosis, principally among families of unrelated Roumanians. The original cases were discovered in 1932 and the latest death occurred in 1944. Twenty-one persons were examined, 7 being found to have active pulmonary disease of whom 4 died of the infection and 2 have active disease in 1944. Only 2 of the infected cases were blood relations.

The fifth and last group contains nine families, five of them related by marriage. Fifty persons were examined, of whom 12 had active tuberculosis either primary or postprimary. The original case seems to be the grandmother in the first family who infected her oldest son. This son in turn infected one of his sons and 5 young persons, all members of unrelated families. One of these young persons became a secondary centre of infection for 2, if not 3 young children, 2 being nieces and the third unrelated to him but a cousin of one of the nieces. The first case was discovered in 1929 and the last in 1944.

Commitment of positive-sputum cases to an institution, relatively easy in larger cities, is very difficult in rural areas. This is due in part to the fact that the part-time health officer is the family physician and in part to the apathy of the public who are unaware of the infectious nature of the disease, believing that heredity plays the most important rôle in the spread of tuberculosis. This leaves persuasion and education as the principal weapons to be used against recalcitrant patients who are unwilling to accept the necessarily long periods of hospitalization.

SUMARIO

En este estudio de la propagación de la tuberculosis, tanto dentro como fuera del hogar inmediato, preséntanse cinco familias o grupos familiares, habiéndose trazado con la mayor exactitud posible, por medio de los protocolos de la clínica, la vía que siguió la infección de una persona a otra. En todos los grupos el porcentaje de exámenes de los contactos es alto, siendo muy pocos los que se negaron a cooperar.

En la primera familia se trazó la enfermedad de la abuela a la hija y a la nieta de ésta, sin casos afuera.

La segunda familia revela, durante un período de 18 años, la infección de ocho de 10 hijos y de todos los nietos, con dos muertes y cuatro casos más que necesitaron asistencia sanatorial. No se descubrió jamás el origen de la infección, pues el primer caso sólo fué descubierto en 1926, o sea antes de efectuarse exámenes intensivos de los contactos.

El tercer grupo comprende dos familias, siendo en la primera la hermana más joven la causa de la enfermedad descubierta un año después en una hermana en la segunda familia. Cuando se hizo el primer examen, ambas hermanas habían muerto y otros dos familiares padecían de tuberculosis activa. Los casos primitivos fueron las dos abuelas y posiblemente la madre, habiendo ya muerto todas.

El cuarto grupo comprende una serie de casos de tuberculosis, principalmente en familias de rumanos no emparentados. Los casos primitivos fueron descubiertos en 1932 y la última muerte sobrevino en 1944. El examen comprendió 21 personas, en siete de las cuales se encontró enfermedad pulmonar activa, habiendo muerto cuatro de la infección y teniendo dos la enfermedad en forma activa en 1944. Sólo dos de los casos infectados eran parientes.

El quinto y último grupo comprende nueve familias, cinco de ellas emparentadas por casamiento. Se examinó a 50 personas de las cuales 12 tenían tuberculosis activa, bien primaria o postprimaria. El caso primitivo parece haber sido el de la abuela en la primera familia, quien infectó al hijo mayor, él que a su vez infectó a uno de sus hijos y a cinco jóvenes más que pertenecían a otras familias. Uno de esos jóvenes se convirtió en un foco secundario de infección para dos, si no tres, niños pequeños, dos de ellos sobrinos, y el tercero no emparentado con él, pero sí primo de uno de las sobrinas. El primer caso fué descubierto en 1929, y el último en 1944.

En las zonas rurales resulta muy difícil hacer llevar los casos de esputo positivo a alguna institución, lo cual es relativamente fácil en las ciudades grandes. Esto se debe en parte a que el médico de sanidad de tiempo parcial es también el médico de la familia, y en parte a la apatía del público que no se da cuenta de la naturaleza infecciosa de la enfermedad, por creer que la herencia desempeña el papel más importante en la propagación. Esto convierte la persuasión y la educación en las armas principales que hay que utilizar contra los enfermos recalcitrantes que se niegan a aceptar los períodos forzosamente largos de hospitalización.

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EPIDEMIOLOGY OF TUBERCULOSIS IN A MENTAL HOSPITAL¹

DAVE B. RUSKIN

The death rate from tuberculosis in institutions for mental diseases and mental defects has been reported to be twelve times that for the population as a whole (1, 2). This high death rate has been prevalent for years. Various investigators (3, 4) have commented on the overcrowding of mental patients and the carelessness of these patients in matters of personal hygiene as influencing this high incidence of tuberculosis. The greater degree of contact between persons comprising an institution population complicates the problem of tuberculosis control and results in a greater possibility of the spread of infection. The increase of tuberculous infection among patients according to the length of hospitalization has been demonstrated (3, 5, 6), and the inference drawn that many patients contracted tuberculosis after admission to the hospital (1), there being ample opportunity for cross infection (7).

Several epidemiologists have concluded that susceptibility to tuberculosis is not related to the type of mental disorder, except insofar as the mental disorder affects the length of residence in an institution. Plunkett (8) points out that environmental factors play a more common part in the spread of this infection than constitutional factors.

McCain's (9), Fellows' (10), and Heise's (11) findings fit in quite well with the reasonably well established opinion that, after the reinfection type of tuberculosis has produced lesions sufficiently large to be seen in the roentgenogram, there is a period of two or three years before symptoms appear. When symptoms do appear, about 80 per cent of the patients are either in the moderately advanced or far advanced stages. Those who have had experience with mentally abnormal patients can fully appreciate how much more difficult it is to elicit complaints from them than from patients who are mentally normal.

Deegan, Culp and Beck (1) state that it was noted that the highest incidence was in the more deteriorated patients in whom factors of personal hygiene and the general character of the surroundings would seem to be of importance. Discussing the dementia praecox patients, they state that prolonged hospitalization in a tuberculous environment, rather than a specific lack of resistance, is thought to be the dominating epidemiological factor. They say further that segregation of the known cases of tuberculosis greatly reduced the health hazard, but roentgenographic reëxamination of the previously negative patients revealed a high incidence of new disease and infection. These results might have been caused by exposure to open cases of tuberculosis prior to the completion of segregation.

The result is that pulmonary tuberculosis comes to the attention of the physician through symptoms indicating advanced disease. The hopeless prognosis and the possibility of spread are too obvious to require discussion (6).

After studying the results obtained by the use of all the recognized methods

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of diagnosis, most investigators have selected the roentgenogram as the most reliable method. Blalock and Funkhouser (13) conclude that the best method of diagnosis (of tuberculosis) in the mentally ill is roentgenographie. All patients of one hospital, except those known to be tuberculous, received an intracutaneous test of Old Tuberculin and 86.6 per cent reacted (1). This prompted Deegan, Culp and Beek to examine roentgenographically the chests of the entire patient population rather than the reactors only. Deegan, Beek and Culp (14), by this method, determined the presence of tuberculous disease or infection in 20.3 per cent of all patients examined (reactors and nonreactors).

Burns (5) points out that the success of the entire case-finding program depends on the prevention of the spread of the tubercle bacillus by segregation of cases already infectious, and by discovery and treatment of early cases before they have become infectious. Plunkett, Weber, Siegal and Donk (12) claim that every case of reinfection type tuberculosis could be associated with the presence of an infectious case in its immediate environment and that, on the other hand, not one case of reinfection type of tuberculosis developed among inmates who at no time were associated intimately with an open case of tuberculosis.

The need for added isolation facilities in state hospitals, asylums and schools for the feeble-minded and epileptic constitutes a very serious problem, not only because of the number of cases, but also because of the mental condition of the patients (5).

MATERIAL

Early in 1937, it was noted by the staff of the Caro State Hospital that many patients were being hospitalized for the care of tuberculosis. These patients had all been diagnosed following the onset of respiratory symptoms and consequently, for the most part, were advanced cases. Accurate data concerning the incidence of tuberculosis in the patient population were entirely lacking. A preliminary survey of the practices followed, in diagnosing tuberculosis, suggested the possibility that there were many unrecognized active tuberculous patients. This suspected high prevalence of tuberculosis in the patient population was confirmed on reviewing the patient deaths from 1931 to 1937, when it was noted that tuberculosis was reported as the cause of death in 66 (14.2 per cent) of the 473 patients who died in that period.

The problem resolved itself into three phases: (a) a tuberculosis survey of the patient population; (b) an examination to determine the presence of active tuberculosis among newly admitted patients; and (c) a program of segregation and care of all patients with active tuberculosis.

At the initiation of the survey there were two wards, one for men and one for women, in the hospital building, for the segregation and treatment of the then diagnosed patients with active tuberculosis. The remainder of the hospital building was occupied by acutely ill and bedridden patients. There were nine cottages for the ambulatory patients, of which Cottage 1 was occupied by boys, Cottages 2, 3, 5, 7 and 9 by men and Cottages 4, 6 and 8 by women. There

were housed also a small group of girls at Cottage 6. The patient population was approximately equally divided as to sex. The mentally most inferior patients were housed in Cottages 2, 7 and 9 for men and 6 and 8 for women, with Cottage 1 housing boys of varied mental levels.

Intracutaneous testing was started in June, 1937. Old Tuberculin diluted 1:1000 and 1:100 was used, as it was originally planned to do a preliminary screening and to examine roentgenographically the reactors only. The extremely high incidence of tuberculous infection as indicated by the tuberculin reactor rate, as applied to one cottage, prompted us to examine the chests of the entire population roentgenographically, rather than the reactors only. Patients whose roentgenograms showed evidence of tuberculosis were studied further in an attempt to evaluate their dynamic status. Such study included serial and stereoscopic films as indicated, and the examination of the sputum and gastric contents for acid-fast bacilli, when possible. However, since it was often difficult to get adequate sputum specimens we were forced, in most cases, to judge activity by roentgenographic findings alone. We have classified our findings into (1) negative, (2) inactive and (3) active. The inactive group contained all those showing (1) evidence of pulmonary tuberculosis in the arrested stages according to the National Tuberculosis Association standards, (2) parenchymal fibrotic or fibrocalcific infiltration and (3) solitary parenchymal or hilar calcified nodes or both.

The work was carried on by the Hospital staff and the interpretations of the roentgenograms were made by the staff of the Division of Tuberculosis of the Michigan Department of Health. The diagnoses were made within the limits of broad roentgenographic interpretation. During this interval—December, 1937 to December, 1943—there were 355 deaths including 64 (18 per cent) deaths of tuberculosis patients. One hundred fifty-one postmortem examinations were made, of which 31 (20 per cent) were on deceased tuberculous patients. Post-mortem examinations have confirmed the clinical diagnoses in a high percentage of cases.

The roentgenographic studies were started on December 1, 1937, at which time there were 1,007 patients in the institution. From the date when this survey started, all patients were examined roentgenographically on admission, and only those considered not to have an active lesion in the lung were transferred to one of the cottages. During the six-year period from December 1, 1937 to December 1, 1943, there were 961 admissions of which 85 were received from other state hospitals accompanied by reports of recent roentgenograms of the chest, 69 were received from the same hospitals without any such reports and 47 admissions did not undergo study because of removal or death shortly after admission. In all, a total of 1,852 patients were roentgenographically examined during this six-year period.

Since the survey was completed, no plan of follow-up had been used and diagnosis again depended upon roentgenographic interpretation after clinical symptoms were evident. As in all other institutions, some patients are examined roentgenographically from time to time for various complaints and, thus, over a period of

years many will have had their chests examined a variable number of times at varying intervals. In considering this group, serial roentgenograms and multiple roentgenograms during a single illness were considered as a single roentgenogram. The period between the separate or serial roentgenograms was over six months and, in many cases, a few years.

The patients found to have active tuberculosis were segregated from other patients by isolation in the two aforementioned wards in the hospital building. Their care was under the supervision of all the doctors on the Hospital staff, none of whom is especially trained in the treatment of tuberculosis, and attended to by the regular employees in that building, whose services on the various wards were rotated so that each employee, in turn, served for a period of four months on one of the tuberculosis wards. These employees were examined roentgenographically, before and after each period of service.

Our therapy on these wards was limited to the experience of the staff physicians and by the coöperation of our patients. Artificial pneumothorax was the only method of collapse therapy which we have found practical to use with these patients. It has been our experience that, when coöperation by the patient is obtainable, mentally ill patients react fairly well to routine bed-rest and a well balanced nourishing diet. When the disease becomes arrested,² the patient is moved to another ward in the hospital where he is started on exercise and if, on close observation, there are no signs of reactivation, the exercise is increased. Should his condition remain arrested, he is discharged to a cottage in six months, after which he is followed from time to time by clinical and roentgenographic observation.

FINDINGS

Examination of the roentgenogram reports revealed that 1,527 (82.45 per cent) of the total 1,852 patients examined showed no evidence of pulmonary tuberculosis, 191 (10.31 per cent) were considered to have inactive tuberculosis (following serial X-ray films) and 134 (7.2 per cent) had active tuberculosis.

Of the 134 patients with active tuberculosis, 15³ (0.8 per cent of the total number of patients examined) had been diagnosed as such before the survey and had been isolated in the hospital building. Table 1 shows that 93.2 per cent of of this group were in the moderately advanced or far advanced stage when diagnosed. Also, of this group, 53.2 per cent are dead, all having died of tuberculosis.

Table 2 reveals the distribution of these patients by age groups and by length of residence before diagnosis was made. Seventy per cent were found to have been under 40 years of age at time of diagnosis and 73.3 per cent were in residence five years or less at time of diagnosis.

² Since it is impossible to prevent a minimum of activity among our patients while on the tuberculosis wards, the exercise to which the patient is introduced, on transfer from these wards, is more advanced than one would find in other hospitals or sanatoria. Therefore, the term arrested is used advisedly in this instance although in the strict sense such exercise should precede its use in diagnosis.

³ Original group.

TABLE 1

Prevalence and stage of tuberculosis in the various groups studied

GROUP DIAGNOSED	NUMBER IN GROUP	STATE OF DISEASE AT TIME OF DIAGNOSIS IN PER CENT OF GROUP			PRESENT STATUS IN PER CENT OF GROUP		
		Minimal	Moder- ately advanced	Far advanced	Arrested	Active	Deceased
Original tuberculosis pa- tients.....	15	6.6	26.6	66.6	33 ¹	20.0 ¹	53.3
Tuberculosis discovered in survey.....	54	20.4	42.5	37.0	37 ²	27.7 ²	46.3
Diagnosed on admission...	16	31.3	68.8		31.3	43.7	25.0
Diagnosed in subsequent films after survey:							
First film.....	35	25.7	28.5	45.7	25.7 ¹	22.8 ¹	54.2
Second film.....	10	20.0	50.0	30.0		30.0	70.0
Third film.....	2	50.0	50.0		50.0	50.0	
Fourth film.....	1			100.0			100.0
Fifth film.....	1	100.0			100.0		
Total number of active tuberculosis.....	134	22.3 ⁴	40.2 ⁴	37.3 ⁴	29.8 ^{3,4}	25.3 ^{3,4}	47.7 ^{3,4}

¹ One case was arrested only to become active later.² Two cases were arrested only to become active later.³ Four cases were arrested only to become active later.⁴ These figures are an expression of the percentage of the total 134 patients and not the total of the percentages in their respective columns.

TABLE 2

*Classification of original group of tuberculosis patients by age and residence**Years of residence before diagnosis*

AGE	1	2	3	4	5	6	7	8	9	10	11 to 15	16 to 20
<i>years</i>												
0-4												
5-9	1											
10-14		1	1									
15-19		1	1		1							
20-24					1							
25-29				1	1							
30-34	1										1	
35-39				1								
40-44												
45-49												
50-54											1	2

Further study of the pre-diagnosis residences of these original tuberculous patients revealed that a greater number of them had lived in one or more of

Cottages 1, 7 and 8. These cottages represented those patients who, in the aggregate, functioned at the lowest level of efficiency among the children, men and women of the institution, with the exception of those in Cottage 2. This latter cottage, alone, fails to follow the parallelism drawn between the incidence of tuberculosis and the functional efficiency of the patients. This exception may be ascribed to the fact that the patients of this cottage were so functionally deficient as to provide a certain amount of segregation merely by their inability to mingle among themselves.

The survey was not completed for over a year. At the end of that time, 54⁴ new cases, 2.91 per cent of the total population, had been discovered among the apparently well resident patients. We found that, by roentgenographic studies

TABLE 3

Classification of the survey group of tuberculosis patients by age and residence
Years of residence before survey and diagnosis

AGE	1	2	3	4	5	6	7	8	9	10	11 to 15	16 to 20	21 to 25
<i>years</i>													
0-4													
5-9													
10-14		2			1								
15-19	3	1	1	1									
20-24	2			2	3	3	1				1		
25-29					1	2	1		2		2		
30-34						1	1				1	1	
35-39		1					3	1		1	2	2	
40-44									1		1		1
45-49												1	1
50-54							1						
55-59					1						1		
60-64												1	
65-69											1		
70-75							1						

before clinical symptoms were apparent, the percentage in the moderately advanced and far advanced cases was 79.5 per cent. This finding is significant, inasmuch as there was a drop of 29.6 per cent in the far advanced cases as against a drop of 13.7 per cent in the total of moderately and far advanced cases combined. Table 1 reveals that in this group we have 46.3 per cent dead as against 53.3 per cent dead in the original group. Although the numbers are too small and the numerical differences are too slight for one to draw a conclusion, there is a definite impression, as shown in the table, of an improved prognosis for the group diagnosed before clinical signs and symptoms are evident.

As compared to the original group, the survey group (table 3) presented a definite shift towards the older patients and also to that group of patients in

⁴ Survey group.

residence over five years. Thus many of these patients may have been asymptomatic, open cases, sowing the seed of tuberculosis long before the majority of the original group had ever been admitted to the institution. And many of the latter may well have become tuberculous after admission by being infected by one of these patients found years later in the survey.

Study of the survey group according to cottages reveals again a parallelism between the type of cottage resident and the incidence of tuberculosis, with one exception. In the survey group may be found a high prevalence of tuberculosis among the residents of Cottage 4, which housed patients functioning at a relatively high level. Due to their higher level of function, many of these patients were used as attendant helpers in Cottages 6 and 8 and thus were in intimate contact with the patients of these latter cottages. Thus one might think that the cottage segregation of the Cottage 4 patients was more than offset by their patient contact during the day's activities while working in Cottages 6 and 8.

There is, with the exception of Cottages 2 and 4, a rough parallelism in the incidence of tuberculosis by cottage, between the original group and the survey group.

Among the newly admitted patients, 16⁵ (0.9 per cent of the total population and 1.7 per cent of the new admissions) were found to be tuberculous. Only a fraction of those diagnosed on admission presented a history of tuberculosis. Of these patients, none was in the far advanced stages; only 25 per cent are dead, of which one (6.2 per cent) died of a cause other than tuberculosis (table 1); all were under 45 years of age, 3 were under 5 years of age and the remainder from 15 to 45 years of age.

Since the survey was completed, 49⁶ (2.7 per cent of the total population) others cases of tuberculosis were discovered among the previously negative and inactive patients during the past five years. No method of follow-up had been used during this period and diagnosis again depended upon roentgenographic interpretation after clinical symptoms were evident. Thirty-five (71.4 per cent) of the 49 (table 1) were discovered on their first film after survey, 10 (20.4 per cent) of the 49 were examined roentgenographically twice after the survey before active tuberculosis became evident. Two (4 per cent) of the 49 were diagnosed after three examinations following the survey, one (2 per cent) was diagnosed after being examined four times and one (2 per cent) was diagnosed after being examined five times following the survey.

Table 1 will also disclose a smaller yield of far advanced cases with an increase in the frequency of roentgenographic examination with the exception of one patient. This patient, diagnosed in the far advanced stage, had been under treatment for a chest disease, type undetermined, for over a year before the specific diagnosis was made.

Table 4 shows these 49 diagnosed cases according to the age and length of residence after the survey.

Further studies reveal that the highest contributory incidence by cottage was from those cottages in which the patients functioned at the lower levels.

⁵ Admission group.

⁶ Subsequent group.

Between May, 1940, the date when six new cottages were opened, and the present date, a few tuberculous patients were found in these new cottages. These patients had, however, all lived for an appreciable length of time in one or more of the cottages already discussed. Thus we have 49 patients with tuberculosis who were roentgenographically tuberculosis-negative or inactive before December 1, 1938, most of whom became open cases within the next three years and whose residence can be traced to the same cottages which contributed so highly in the original and survey groups.

Of the 134 patients diagnosed as tuberculous, 64 (47.7 per cent) are deceased and 45 (25.3 per cent) are still active (table 1).

TABLE 4

Classification, by age and residence, of tuberculosis patients following the survey and before diagnosis

Years of residence following survey

AGE	1	2	3	4	5
<i>years</i>					
0-4	1				
5-9	1	1			
10-14	2		1		
15-19	4	2	1		
20-24	3	2		2	
25-29		1		1	
30-34	1	1	3		1
35-39	2	2	2		
40-44					
45-49		1	2		
50-54	3	2			
55-59	1	1			
60-64	1				
65-59	1	1	1		1

COMMENT

The foregoing has been offered to show that, under conditions prevailing at the Caro State Hospital during the past six years, conditions which we feel will be found in most state owned hospitals throughout the country, the death rate for tuberculosis is disproportionately high. This high death rate naturally follows the lack of a program which serves to uncover active tuberculosis before the infection has had an opportunity to spread. The incidence is neither due to a specific lack of resistance nor parallel to the severity of the mental condition. The incidence does parallel the opportunity for intimate contact in an environment rich in patients with active tuberculosis.

The problem develops from two main roots: the introduction of cases through commitments and the development of new cases through exposure in the institution. The lower incidence rate among newly admitted patients reveals the value of roentgenographic examination on admission. This incidence rises

with the duration of institutional residence and opportunity for intimate contact between nontuberculous and undiagnosed tuberculous patients.

The problem of control resolves itself into detection and segregation of patients with pulmonary tuberculosis. These patients should be segregated from those who show no evidence of tuberculosis other than a positive skin reaction. This segregation and accurate evaluation of the clinical status of these persons permit the use of proper nursing techniques and modern methods of treatment. There must be repeated, preferably annual roentgenograms of the patients not showing active tuberculosis, to find promptly the patient who is breaking down with clinical tuberculosis.

The problem presented in the epidemiology of tuberculosis is more complex than that of almost any other of the common diseases. The contagious technique required is difficult as a part of an administrative unit of the average state mental hospital. Several questions involving the administrative control of the disease become important. Unless definite control measures are taken, such institutions may become reservoirs of infection. The communicable disease problem superimposed upon the mental problem results in the former becoming of paramount importance, and the care of patients with active tuberculosis should not be the responsibility of a hospital for the mentally ill. Isolation of these patients in a separate institution should be provided in order that contagious technique can be given first place in the management of the sick and in order that the public health problem involved may not be overlooked in the institutional routine. Return of these patients should be made dependent upon their convalescence to the point where there is no longer a public health problem involved.

In several states these facilities have been provided under various plans. Each plan involves slightly different methods of administration, but directed at two goals: (1) segregation of mental patients with active tuberculosis, and (2) administration and care of such a program by men trained primarily in tuberculosis, with some knowledge of psychiatry.

In post-war planning, which is the popular activity of practically all governmental and nongovernmental organizations, this problem of tuberculosis care deserves a prominent place.

SUMMARY

A study of the prevalence of tuberculosis in a state-owned hospital for epileptics was presented. Factors influencing the high incidence were discussed. Suggestions were made whereby the prevalence rate could be lowered. The epidemiology and public health hazard of tuberculosis in a mental (epileptic) hospital were discussed. The advisability of special hospitals for tuberculous inmates of mental hospitals was suggested.

SUMARIO

Este trabajo versa sobre la incidencia de la tuberculosis en un hospital del Estado para epilépticos. Discútense los factores que afectan la elevada incidencia y se ofrecen indicaciones para hacerla descender. También se repasa

la epidemiología y el riesgo sanitario que entraña la tuberculosis en un hospital de casos mentales y se indica la conveniencia de establecer hospitales separados para los tuberculosos reclusos en los hospitales para psicópatas.

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BRONCHOGRAPHY IN PULMONARY TUBERCULOSIS¹

VI. Thoracoplasty

Part 2

B. A. DORMER, J. FRIEDLANDER AND F. J. WILES

Group II. Unsuccessful Cases

Case 10: E.541, European male, aged twenty-five years. His disease began one year before admission with cough. Two months later he felt weak and lost his appetite. He reported sick and pulmonary tuberculosis was diagnosed. He is a thin, ill looking man. His temperature and pulse are normal. Sputum contains tubercle bacilli. The physical signs are dulness over the whole of the right side with distant bronchial breath sounds and crepitations.

An X-ray film showed extensive disease throughout the whole of the right lung and upper lobe cavitation.

An artificial pneumothorax was not successful. A full thoracoplasty was therefore performed in three stages. A bronchogram showed a residual bronchiectasis and a lateral bronchogram confirmed this diagnosis.

The patient's sputum was positive after the last operation and has remained so for the last two years. He is no longer in our care so we are unable to try intrabronchial treatment.

Case 11: E.199, European male, aged thirty-five years. His illness began twenty years ago. His sister died of tuberculosis and he was examined as a contact and told he had minimal disease. He carried on with his ordinary life for eighteen years until he had an hemoptysis. He then had an artificial pneumothorax induced and this was followed by a tuberculous empyema. He is an ill looking European male. His temperature and pulse are normal. Sputum contains tubercle bacilli.

An X-ray film showed a partially collapsed right lung and a hydropneumothorax. Aspiration revealed pus which contained tubercle bacilli.

A thoracoplasty was commenced, but the patient, after the first stage, refused further treatment and left the hospital. He returned some months later and a second stage was eventually done.

A bronchogram (figure 18) shows a bronchiectatic right upper lobe and an extensive bronchiectasis in an atelectatic lower lobe. Even if the thoracoplasty had been much more efficient this lower lobe bronchiectasis would not have been collapsed.

Sputum was positive after the operation and it remained so for two years, during which time the patient was back at work. He died suddenly of an intercurrent infection leading to a streptococcal septicemia.

Case 12: E.219, European female, aged thirty years. She has been coughing for twelve years, and tuberculosis was diagnosed ten years ago. She has had no treatment. She is an ill looking, cyanosed woman with normal temperature and pulse. Sputum contains tubercle bacilli. Physical signs are dulness with bronchial breathing and crepitations over the left upper lobe. There are signs of a cavity in the left infraclavicular region. Crepitations are present in the right upper lobe.

¹From the King George V Hospital for Tuberculosis, Durban, South Africa.

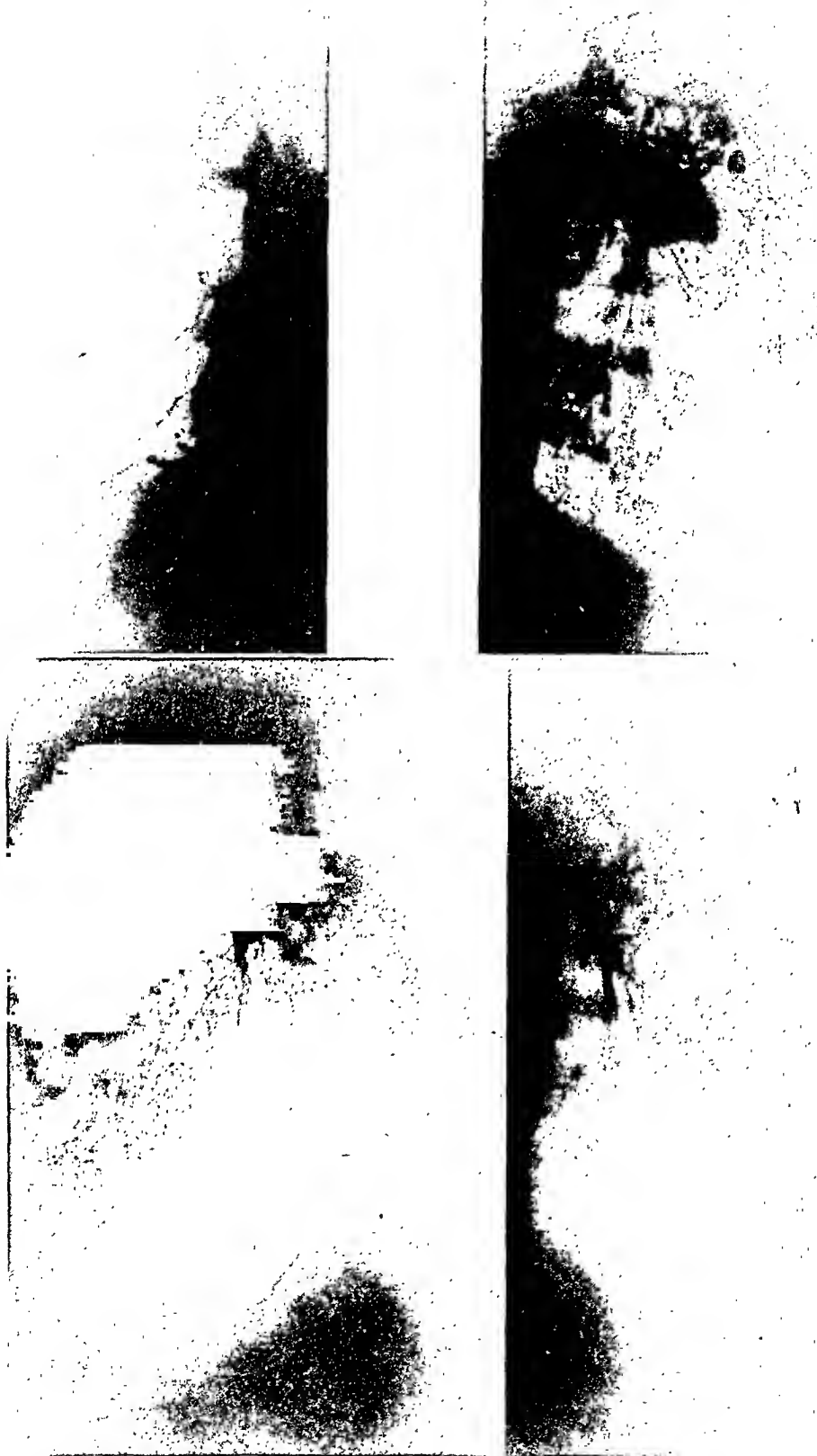


FIG. 18. Upper left; FIG. 19. Upper right; FIG. 20. Lower left; FIG. 21. Lower right.

An X-ray film showed old-standing disease of the left upper lobe with a large cavity in the infraclavicular region, approximately $2\frac{1}{2} \times 2$ inches. There was some clouding of the right apex. A bronchogram (figure 19) shows a thick pleura over the left upper lobe which is atelectatic and the seat of massive bronchiectasis and cavitation; there is normal filling of the lower lobe with marked upward pull of the bronchi by the atelectatic upper lobe. A lateral picture (figure 20) shows the depth localization of the bronchiectasis and cavitation.

A two-stage thoracoplasty was done on the left side and a bronchogram (figure 21) shows the bronchiectasis still present.

The patient's sputum remained positive throughout, although in all fairness it must be pointed out that there was probably some active disease of the right apex.

Case 13: E.460, European male, aged forty-four years. He was coughing for two years and took no notice of it. He had an acute appendicitis about six months ago and, because his cough was troublesome after this, he was X-rayed and pulmonary tuberculosis diagnosed. He is a fat, fit looking man. His temperature and pulse are normal. Sputum contains tubercle bacilli. The physical signs are those of a cavity at the right apex. There are a few crepitations at the left apex.

An X-ray film showed chronic fibroid phthisis of the right upper lobe. The patient was excessively obese and the interpretation of the rest of the plate was difficult. A bronchogram (figure 22) shows atelectasis and bronchiectasis of the right upper lobe and normal filling of the rest of the lung.

A two-stage thoracoplasty was done and a bronchogram (figure 23) shows that the bronchiectasis remains in spite of the thoracoplasty. Following the operation the sputum remained positive. He is being treated by intrabronchial application of sulphonamide suspension in lipiodol.

Case 14: C.39, colored male, aged forty-one years. About a year ago he had cough and consulted his doctor who diagnosed pulmonary tuberculosis. He spent seven and a half months in a hospital and attended a tuberculosis clinic as an out-patient for some time before being readmitted. He is a healthy looking colored male. His temperature and pulse are normal. Sputum contains tubercle bacilli. Physical signs are those of moderate dullness with harsh breath sounds and a few crepitations over the right upper lobe.

An X-ray film showed mottling of the right apex, extensive infiltration of the right base with a cavity at the root, one inch in diameter. There was some scattered mottling on the left side, especially in the midzone and base.

In view of the cavity on the right and its situation, the first line of treatment was a phrenic crush on this side. X-ray examination after the operation showed considerable clearing on the right.

As the sputum still contained tubercle bacilli, a bronchogram (figure 24) was done, and this revealed a system of cavities not visible on the ordinary X-ray plate.

An attempt at an artificial pneumothorax was not successful, so a thoracoplasty was done. Figure 25 is a bronchogram following the operation. There is still extensive bronchiectasis and cavitation.

The patient's sputum remained positive and he had a sudden hemoptysis almost a year after the last stage and died in one or two minutes.

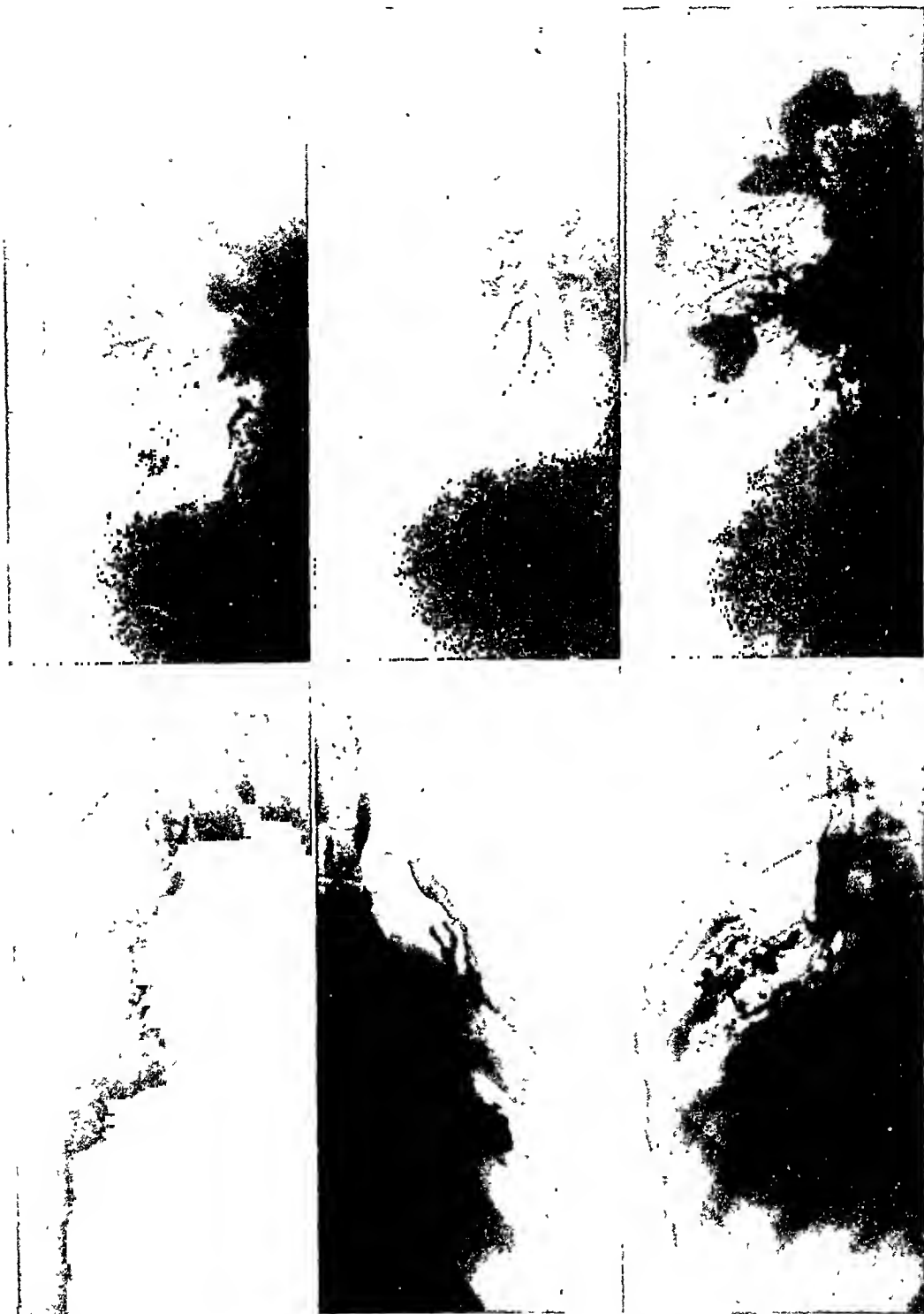


FIG. 22. Upper left; FIG. 23. Upper centre; FIG. 24. Upper right; FIG. 25. Lower left; FIG. 26. Lower centre; FIG. 27. Lower right.

This case is valuable in that it shows the importance of a bronchogram after a phrenic operation and the obvious desirability of doing this form of investigation before this or any other form of operation.

Case 15: E.251, European female, aged thirty-three years. About a year before admission she began to have headaches and tire easily. She became feverish with shivering attacks and severe sweats at night. Then a pain developed on the right side and she was admitted to a hospital with a high temperature. The cause of the illness proved to be a tuberculous pneumonia and she was eventually sent to a sanatorium where she felt better for a while until her cough became troublesome. She is a frail looking European female. Temperature is between 99 and 100°F.; pulse 90 to 120. Sputum contains tubercle bacilli. Physical signs are dulness with bronchial breathing over the left upper lobe and crepitations throughout the left side..

An X-ray film showed a large cavity occupying the area of the left upper lobe and an obscured left base. An artificial pneumothorax was attempted but was unsuccessful.

A two-stage thoracoplasty was performed. This appeared to have dealt with the cavity most satisfactorily but the patient's sputum still contained numerous tubercle bacilli.

A bronchogram (figure 26) shows the extensive residual bronchiectasis.

Some months later the patient had an acute spread of disease on the right side and died.

Group IIA

This subgroup contains two examples of extensive lower lobe bronchiectasis in patients who appear, on ordinary X-ray films, to have only an upper lobe cavity. Both these patients died before completion of their thoracoplasties. We know from bitter experience, however, that even a total thoracoplasty is of no avail in this type of case.

Case 16: E.145, European female, aged twenty-seven years. Her disease began nine years ago with pneumonia and pleurisy. She had a spell in a sanatorium and remained well for nearly seven years when she developed an acute appendicitis. Following this operation her cough was troublesome and she was X-rayed and told her disease was again active. She is a thin, ill looking woman. Temperature is between 97 and 98.4°F.; pulse 84 to 92. Sputum contains tubercle bacilli. Physical signs are dulness over the whole of the right lung and signs of a large cavity with crepitations in the upper lobe. The apex beat is to the right of the sternum.

An X-ray film showed a large cavity occupying the area of the right upper lobe and an obscured base. There were scattered small calcifications through the left lung.

A first-stage thoracoplasty was performed on the right side. A bronchogram (figure 27) shows the unexpected bronchiectasis at the base on the right.

A second stage was done, but the patient died on the tenth postoperative day.

Case 17: E.104, European female, aged thirty-seven years. About two years prior to admission she developed a cough and then a month later had a large hemoptysis. She was treated at a sanatorium for eighteen months. She is a fit looking woman. Her temperature and pulse are normal. Sputum contains tubercle bacilli. The physical signs are dulness over the whole of the left lung with deficient air entry and numerous crepitations throughout.

An X-ray film showed a large cavity in the left upper lobe and the rest of the left lung was obscured. The heart and mediastinum were pulled over to the left.

A first-stage thoracoplasty was performed. A bronchogram showed the actual nature of the disease at this stage. Besides the upper lobe cavity there was an extensive bronchiectasis occupying the whole of the lower lobe. Further operative interference was not attempted, and the patient subsequently died from a spread of the disease to the other lung.

SUMMARY AND CONCLUSIONS

1. Seventeen cases of pulmonary tuberculosis treated by thoracoplasty are described.

2. From a study of their bronchograms the conclusion is reached that in most cases it is a matter of chance whether the operation results in a negative sputum or not.

3. It is suggested that an intrabronchial attack is a logical treatment in pulmonary tuberculosis, and the use of a suspension of sulphonamide in lipiodol is described.

SUMARIO Y CONCLUSIONES

1. Describense 17 casos de tuberculosis pulmonar tratados con la toracoplastia.

2. De un estudio de las broncografías dedúcese que en la mayoría de los casos es puro azar el que la operación resulte o no en negativación del esputo.

3. Indícase que el ataque intrabronquial constituye un tratamiento lógico en la tuberculosis pulmonar, y describese el empleo de una suspensión de sulfonamidos en lipiodol.

This being the last of this series of articles on bronchography in tuberculosis we wish to express our gratitude to those who have assisted us with the work. We wish particularly to express our gratitude to Dr. Max Pinner for editing and proof-reading these articles and for his interest and encouragement in our work; to Mr. M. Gibson and Mr. R. Sadler for reproducing the X-ray plates; to Sister A. Sawdon for her help with thousands of bronchograms; and to Miss M. Childs for her invaluable secretarial work.

Homer L. Sampson

1880-1945

Homer L. Sampson was born in New York City April 4, 1880. There he attended public school but left short of graduation to become a cash boy in a mercantile house. His advancement was steady for eighteen years until at thirty years of age his health became impaired. During his working years he had photography as a hobby. He was married in 1908.



Homer L. Sampson

1880-1945

He arrived at the Adirondack Cottage Sanitarium on September 10, 1910. After completing his treatment, he worked as instructor in photography in the patients' rehabilitation workshop and in 1912 was appointed to operate the newly acquired X-ray machine. Without assistance he studied physics, electricity, anatomy, physiology and pathology. He has written many articles

on the use of the X-ray in tuberculosis and was co-author of a treatise on intestinal tuberculosis. He addressed many societies, both clinical and X-ray. He designed an octagon revolving stereoscope. In 1933 he received the honorary degree of Doctor of Science from the University of St. Lawrence. Several years ago he was appointed consultant in the Department of Radiology at the University of Rochester and consulting roentgenologist at St. Joseph's Hospital in Ogdensburg. He has been a member of the Federal Department of Labor, the Medical Committee for the Study and Control of Silicosis and of the subcommittee for the Medical Study and Control of Silicosis in New York State. He was a member of the National Tuberculosis Association, American Sanatorium Association and the Saranac Lake Medical Society; an honorary member of the American Trudeau Society; a teacher in the Trudeau School of Tuberculosis; Roentgenologist for the Trudeau Sanatorium and the Trudeau Foundation. He died May 16, 1945.

Homer L. Sampson was a man of great physical energy, possessing a mind full of curiosity and an outstanding devotion to detail. He was skilled in many crafts and his completed work always possessed the mark of a skilled artisan. He had great patience but always was ready to enter into intelligent discussion and argument to press home his own deductions and to learn the attitude of his associates. He was kindly and generous and gave of his time to all whom he thought he could help. He was associated with many civic movements such as the Rotary, Boy Scouts, Curling Club and the Presbyterian Church. In all he attained to high office and frequently was the motive force to carry on.

So, too, in his work he applied himself diligently and became an expert on radiography in tuberculosis and industrial chest diseases. His accomplishments bear the mark of a genius. For his accomplishments we all give him honor and will remember him for years to come.

But by his associates and the many medical interns and students who have come in contact with him during their stay at Trudeau Sanatorium, as patients and staff members, he will be remembered best for his untiring efforts in their behalf. His interest and his devotion to teaching them what he knew will ever last in their memory. Untiring, unselfish, ever willing beyond the usual day's work to help them gain knowledge.

Trudeau Sanatorium has lost one of its pioneers, a genius, one whose stamp of character always will remain pressed upon its escutcheon.

FRED H. HEISE

AMERICAN TRUDEAU SOCIETY

The Executive Committee of the American Trudeau Society announces with sincere regret the death of the following members during the past year.

Ferdinand Chenik, M.D.
Detroit, Michigan

Estes Nichols, M.D.
Portland, Maine

Charles H. Cocke, M.D.
Asheville, North Carolina

Charles R. Reynolds, M.D.
Chicago, Illinois

R. L. Cunningham, M.D.
Los Angeles, California

Hugh F. Ringo, M.D.
Milwaukee, Wisconsin

Francis DeCaria, M.D.
Bradford, Pennsylvania

*Joseph E. Seliady, M.D.
Northville, Michigan

John W. Flinn, M.D.
Prescott, Arizona

Frank W. Shelton, M.D.
Independence, Kansas

Ralph F. Harloe, M.D.
Brooklyn, New York

Michele Sicca, M.D.
Brooklyn, New York

David S. Lazare, M.D.
Otisville, New York

Charles E. Walker, M.D.
Sanatorium, Mississippi

John J. Lloyd, M.D.
Rochester, New York

Groesbeck F. Walsh, M.D.
Fairfield, Alabama

Edward S. McSweeney, M.D.
New York, New York

†Homer L. Sampson, D.Sc.
Trudeau, New York

*Died in active military service.

†Honorary member.

NOTICE

In November, 1945, there will be held in the City of Buenos Aires the First Argentine Conference on Tuberculosis sponsored by the following scientific societies:

Sociedad Argentina de Tisiología
Sociedad de Tisiología de La Plata
Sociedad de Tisiología de Córdoba
Sociedad de Tisiología de Rosario
Sociedad de Tisiología del Hospital Tornú
Sociedad de Patología Infecciosa y Tuberculosis del Hospital Muñiz
Colegio de Médicos Tisiólogos Universitarios
Liga Argentina Contra La Tuberculosis
Sociedad de Tisiología del Hospital Nacional Central
Sociedad de Médicos de Sanatorios y Hospitales del Valle de la Punilla
Atenco de la Sección Profilaxis y Asistencia de la Tuberculosis
de la Dirección Nacional de Salud Pública
Sociedad de Estudios Científicos para la Tuberculosis del Hospital
Vicente López y Planes

The Executive Committee, formed by the delegates from the above mentioned societies, is comprised of the following members:

President: Dr. Raúl F. Vaccarezza
Vice-Presidents: Dr. Oscar P. Aguilar
Dr. Antonio Cetrángolo
Dr. Francisco R. D'Ovidio
Dr. Justo López Bonilla
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Dr. Amadeo J. Rey
Treasurer: Dr. Ismael M. Hernández
Pro-Treasurers: Dr. José Bellingui
Dr. Luis R. Valle

The official subjects which the Congress will consider are the following:

1. Disability and professional rehabilitation of the tuberculous in the survey of communities.
2. Hematogenous pulmonary tuberculosis.
3. Thoracoplasty in the treatment of pulmonary tuberculosis.
Techniques, indications and ultimate results.

The address of the Secretary is Avenida Vélez Sarsfield 405 (Buenos Aires).

THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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ABST. No. 3

Artifacts in Staining of Tubercle Bacilli.—Evidence is presented to show that the mechanical action of the platinum loop in making smears and of the microtome knife in cutting sections of colonies is sufficient to create non-acid-fast rods and granules. It is not assumed that these observations will refute the existence of some pleomorphism in the reproduction and growth of the tubercle bacillus. There is abundant evidence that, under certain conditions, granular forms and non-acid-fast or weakly acid-fast cells do occur. It is to be emphasized instead that great care should be exercised in the interpretation of stained materials, and especially in the use of staining procedures as measures of experimental results. A large number of films of young growths of *Mycobacterium tuberculosis*, strain H37, prepared without the traumatizing action of a platinum loop or spatula show no non-acid-fast free granules (small or large) or thin rods (long or short). The same results were obtained with *Mycobacterium tuberculosis* H39 RV; *M. tuberculosis* bovine and avian type; *M. phlei*, *M. smegmatis*; *M. ranae* and certain unidentified, nonpathogenic acid-fast organisms isolated from gastric lavage. Films made by spreading the microorganisms as gently as possible with a platinum loop revealed myriads of non-acid-fast granules both large and small, also faintly stained slender non-acid-fast rods of varying sizes which in some cases are attached to granules, non-acid-fast bacilli with deeply stained terminal bodies, and finally typical acid-fast organisms. The percentage of non-acid-fast forms present was found to be roughly proportional to the effort

expended with the platinum loop in making the film. The instrument used for spreading the bacteria was varied with no appreciable difference in results. The cells of older cultures were found to possess a greater resistance to mechanical destruction. In preparations made from thirty-day old cultures of H37 and H37 RV only a few non-acid-fast granules and rods were in evidence, constituting not more than 10 per cent of the total. Sectioning of embedded organisms may also destroy acid-fastness, the non-acid-fast forms are found to be more abundant where distortion of the paraffin is greatest, especially along the marks of nicks or dull places in the knife and the proportion of atypical forms appears to be greater in thin than in thick sections. Sectioning and smearing the cultures produce parallel results, both procedures yielding a greater proportion of non-acid-fast forms from young material. Why the cells from old and young cultures should thus differ is not clear. It could conceivably depend on a differentiated cell wall that might gain in thickness and rigidity as the cell decreases its rate of division and increases in age. The demonstration of the artifact nature of these non-acid-fast fine rods and granules renews interest in the occurrence of similar forms in young microcultures as reported by Kahn. Possibly they do occur, or possibly, as proposed by Oerskov, they are the result of degeneration and crystal formation. It is certain, however, that no support for the existence of such forms in a reproductive cycle can be derived from stained smears or sections of cultures of any age.—*Some Artifacts Encountered in Stained Prep-*

arations of Tubercle Bacilli: I. Non-Acid-Fast Forms Arising from Mechanical Treatment, D. Yegian & K. R. Porter, J. Bact., July, 1944, 48: 88.—(F. G. Petrik)

Cultivation of Tubercle Bacilli.—Comparisons made with Corper's egg-yolk medium without dye or glycerin, Corper's medium with malachite green oxalate and no glycerin, Corper's medium with glycerin and malachite green oxalate, Hohn's medium with and without glycerin and Petragnani's medium, show that Corper's medium was more liable to the growth of contaminants than was Hohn's medium, although it was as efficient for growing small inocula of human type tubercle bacilli. Hohn's medium containing glycerin and dye and at pH 7.0 seems to be the one of choice for routine cultivation of clinical specimens. It is efficient, resists contaminations and provides a good background for early identification of growth of tubercle bacilli. Bovine tubercle bacilli probably would not grow if small numbers were planted on Hohn's medium with glycerin since they do not grow from small inocula on other egg media containing glycerin. The colonies of human tubercle bacilli on Hohn's medium without glycerin are so small, it would not be practicable to use this medium alone for routine clinical work. Possibly some substance could be added to Hohn's medium without glycerin to make it more suitable for growing human tubercle bacilli. Nassau's "blood charcoal" should be investigated for this purpose. It is suggested that one culture medium which is both efficient and dependable would be adequate, provided the clinical specimens are cultured at least in duplicate.—*Cultivation of Human Tubercle Bacilli on Egg Mediums, D. M. Powelson & J. R. McCarter, J. Infect. Dis., July-August, 1944, 75: 95.—(F. G. Petrik)*

Cultivation of Tubercle Bacilli.—Comparative cultural studies were made, using the culture medium introduced by Hohn in 1940 and Löwenstein's egg-medium; 52 sputum specimens, negative on smear, and 53 positive

sputum specimens were cultured on both media. Of the former, 14 positive cultures were obtained on Hohn's and 8 on Löwenstein's medium. The colonies grow faster and are larger on Hohn's medium. The preparation of Hohn's medium is simpler, because the basic mixture can be kept longer in a sterile state. (Lockemann's solution, containing glycerin, 2.7 per cent, with alanin instead of asparagin.)—*Versuche zur Kultur von Tuberkelbacillen auf festen Nährboden, H. Northoff, Diss., 1940.—(G. Simmons)*

Tubercle Bacilli in Feces.—The method for the culture of tubercle bacilli from the feces used in the present study was developed by the author some time ago and is not described in the present paper. Although the number of cases studied is small and the results, therefore, not quite conclusive, it seems that with the method advocated more positive results were obtained than with laryngeal swab, gastric lavage etc. This method is important for the study of intestinal tuberculosis too, because it allows the differentiation of non-tuberculous acid-fast rods of the intestinal flora from true tubercle bacilli.—*Über den klinischen Wert des Stuhlnachweises von Tuberkelbacillen im Verlauf der Lungentuberkulose. Ergebnisse eines neuen Untersuchungsverfahrens, J. E. Wolf, Deutsche med. Wchnschr., 1942, 1: 653.—(G. Simmons)*

Culture Medium for Tubercle Bacilli.—The new medium suggested consists of eggs, potatoes, tomato salad, human plasma and gentian violet. To this mixture an equal amount of a mixture containing asparagin, glycerin, magnesium sulfate, potassium phosphate, calcium phosphate, sodium citrate and ammoniated iron citrate is added. Growth of tubercle bacilli occurs more readily and faster than on the media of Corper-Uei, Hohn, Petragnani and Löwenstein. The inoculation into guinea pigs is still superior to any culture method if the bacilli are virulent. When the virulence is decreased, however, cultures may be positive where the inoculation remains negative. The time when the inoculated animal is sacrificed

is important, because the result may be negative when the animal is sacrificed too early or too late (healing).—*Ein neuer Nährboden zur Schnellkultur des M. tuberculosis. Verschiedenes Verhalten desselben gegenüber den Isolierungs-Nährböden*, O. A. Gimeno, *Rev. españ. de tuberc.*, 1941, 10: 447.—(G. Simmons)

Demonstration of Tubercle Bacilli.—The following material was examined for the presence of tubercle bacilli: 753 sputum specimens, 104 urines, 91 specimens of pus and pleural fluid, 29 spinal fluids, 12 stools, 11 gastric contents. Inoculation into a guinea pig was performed when direct studies were not conclusive. Of the 1,000 examinations, 220, or 22 per cent, were positive with all methods; 175 examinations, or 17.5 per cent, were positive on simple microscopic study. Of 242 animal inoculations, 31, or 14.5 per cent, were positive. Broken down, the results are as follows:

Sputum: 753 specimens,

216, or 28.7 per cent, positive with all methods

125, or 16.6 per cent, positive on smear

79, or 12.1 per cent, positive on concentration

Inoculation was done in 103 specimens, 12 gave positive results.

Pus and pleural fluid: 91 specimens,

24, or 27.9 per cent, positive with all methods

8, or 8.9 per cent, positive on smear

16 positive on guinea pig inoculation.

Urine: 104 specimens, 8 positive, 4 on smear and 4 in the guinea pig

Spinal fluid: 29, one positive on smear and one in guinea pig

Gastric content: 11, 3 positive (28 per cent), 2 on smear and one in the animal

Feces: only one positive in the guinea pig.—

Résultats comparés de la recherche du bacille de Koch par les méthodes de laboratoire dans 1,000 produits pathologiques présumés tuberculeux, P. Hauduroy, *Rev. méd. de la Suisse Rom.*, 1942, 62: 475.—(G. Simmons)

Growth of Tubercle Bacilli in Blood.—Due to different techniques used, attempts to kill tubercle bacilli or to make them less active by means of human or animal blood or its constituents have remained inconclusive so far. It seems, however, that blood taken from a tuberculous individual has a greater bacteriostatic property than that from a normal individual. The experiments were repeated: 0.9 cc. of inactivated rabbit serum was mixed with 0.1 cc. of a bacillary suspension, containing 0.001 to 0.01 mg. of bacilli. The serum acts most favorably on the growth of tubercle bacilli if it is diluted with broth (1:2 or 1:4). The optimum pH for the human strain was 6.5-7.0, whereas germs of the Arloing strain still grow at a pH 6.0-8.5. One day old, not heated guinea pig serum acts more favorably on the growth than serum twenty-one days old. Growth in whole-blood taken from guinea pigs occurs more readily in the thermostat than in the refrigerator. The bacilli grow faster and more regularly in whole blood taken from rabbits or guinea pigs than in the serum prepared from the same bloods. As far as growth is concerned, there is no difference between the blood obtained from rabbits and that obtained from guinea pigs, and it is concluded that the fact that rabbits show greater resistance toward the human tubercle bacillus than guinea pigs cannot be explained on the basis of the existence of protecting substances in the blood of rabbits. Human tubercle bacilli grow better in the blood of healthy guinea pigs than in that obtained from tuberculous animals. Similar experiments with rabbit blood were not conclusive. There is no difference in the growth of the human and the bovine type bacillus in the same rabbit blood.—*Untersuchungen über die Bedingungen des Wachstums von Tuberkelbacillen in tierischem Blut und über entwicklungshemmende Stoffe im Tierblut*, H. Hiroki, *Beitr. z. Klin. d. Tuberk.*, 1942, 97: 664.—(G. Simmons)

Serum Albumin, Food for Tubercle Bacilli.—In the course of studies on the cultivation of minute inocula of tubercle bacilli it was found

that Dorset's synthetic medium with 0.5 per cent human serum albumin performed as efficiently as Corper's egg-yolk medium. Because of its physical and nutritive properties, this serum albumin medium should be an excellent plating medium for research in which the estimation of numbers of viable tubercle bacilli is essential. Growth on the serum albumin media was apparent first in the liquid at the base of the slants and colonies appeared on the slants three to four days later. Growth from 10^{-7} mg. of human type of tubercle bacilli occurred in the 0.05 per cent, 0.1 per cent and 0.5 per cent albumin media and in Corper's medium, and no growth appeared on Dorset's synthetic medium without albumin from the heaviest inoculum. Serum albumin in a concentration of 0.5 per cent stimulated the same amount and rapidity of growth as Corper's egg-yolk medium. The addition of serum albumin to a liquid medium would probably also allow the growth of single cells of human tubercle bacilli.—*Serum Albumin as a Food for Human Tubercle Bacilli*, D. M. Powelson & J. R. McCarter, *J. Bact.*, September, 1944, 48: 479.—(F. G. Petrik)

Fluorescence Microscopy.—This method was found superior in a controlled experiment involving the examination of 300 sputum specimens for tubercle bacilli. Forty-five positive slides were found by this method, as compared to 36 found by the Ziehl-Neelsen technique. Reexamination of the Ziehl-Neelsen slides demonstrated 3 more positive, and preparation of new slides from the same cases, added another 3 positive ones to the Ziehl-Neelsen stained slides, bringing the total positive specimens by the Ziehl-Neelsen stain up to 42. However, slides examined by fluorescence microscopy are examined for six minutes, whereas slides stained by the Ziehl-Neelsen technique are examined for at least fifteen minutes. The saving in time is explained by the fact that there is more contrast between bacilli and background with the auramine-phenol stain when examined with fluorescent microscopy and also, because this is so, a larger objective can successfully be

used and a larger portion of the smear can be examined at one time. Oil immersion is never used for the detection of bacilli by this method. Although this method of examining specimens would seem advantageous for laboratories in which large numbers of sputum specimens are to be examined, a complete switch-over is not advised before parallel experiments have been run. A short experiment such as described in this paper will prove very convincing to all laboratory workers.—*Fluorescence Microscopy in the Detection of Tubercle Bacilli*, H. Lempert, *Lancet*, December 23, 1944, 247: 818.—(H. Marcus)

Subsurface Growth of Tubercle Bacilli.—Suspensions of five virulent strains of *Mycobacterium tuberculosis*, when well dispersed and inoculated into a synthetic medium in amounts of 1 mg. to 10 cc. medium, showed increased turbidity within two days. One avirulent rapidly growing strain grew in a similar manner.—*Subsurface Growth of Virulent Human Tubercle Bacilli in a Synthetic Medium*, G. P. Youmans, *Proc. Soc. Exper. Biol. & Med.*, October, 1944, 57: 122.—(F. B. Seibert)

Infectivity of Mycobacteria.—The results of the implantation of measured doses of 49 strains or species of mycobacteria on the chorioallantoic membranes of chick embryos are given. Organisms of the highest virulence for guinea pigs consistently produce extensive large characteristic lesions in the mesoderm of the chorioallantois, with rapid growth of the bacilli. The character of the lesions differs according to the type of organism, the avian and bovine tubercle bacilli producing a lesion histologically distinct from those caused by human tubercle bacilli of the highest guinea pig virulence. The chorioallantois of the chick embryo varies too greatly in its response to avirulent acid-fast bacilli to make the procedure by itself of value in the determination of the virulence of a given strain or species of organism. The response of the chorioallantois is constant for a given strain or species of organism; variations are chiefly in

degree in individual eggs, not in type or overall extent of the lesions produced. Small doses of bacilli, .01 mg. or less, are by themselves inadequate to show characteristic changes in the membranes routinely. (Authors' Summary.)—*The Infectivity of Mycobacteria for Chorioallantoic Membranes of Chick Embryos*, G. L. Fite & B. J. Olson, *Pub. Health Rep.*, November 3, 1944, 59: 1423.—(P. Lowy)

Atypical Acid-fast Microorganisms.—A qualitative study of the nucleic acid extracted from ten strains of atypical acid-fast bacilli (nonpathogenic for guinea pigs) isolated from sputum and gastric contents of patients with proved or suspected tuberculosis, using Dische's diphenylamine reagents for thymus nucleic acid, indicates that the nucleic acid of four strains consists largely of desoxyribonucleic acid. The material from two other strains gave less color with the reagent, perhaps because of the dilution of the nucleic acid by impurities. It may be, however, that the nucleic acid content of these organisms is a mixture of desoxyribonucleic acid and ribonucleic acid similar to that of *Corynebacterium diphtheriae* which contains both uracil and thymine and is either a mixture of plant and animal types or a new type. No blue color was obtained with the material from the remaining four strains, indicating the absence or a low content of desoxyribonucleic acid. It would appear that any classification suggested for this varied group of microorganisms should include a determination of the nucleic acid content. This work is being continued, employing larger quantities of material to determine quantitatively the types of nucleic acid present.—*Atypical Acid-fast Microorganisms: I. Nucleic Acid Fraction*, F. G. Petrik, *J. Bact.*, September, 1944, 48: 347.—(F. G. Petrik)

Enzymes in Tuberculous Pus.—The glycolytic activity of tuberculous pus is considerable and can destroy 25 per cent of the glucose present. This enzyme originates not only in the leucocytes but also in the plasma. The

amylolytic action of the pus is due to the diastase of the leucocytes. The proteolytic enzymes come mainly from lymphocytes.—*Di alcune azioni enzimatiche contenute nel pus tubercolare*, A. Spandonari, *Arch. méd. e chir.*, 1942, 11: 189.—(G. Simmons)

Pigment Formed from p-Aminobenzoic Acid by Tubercle Bacilli.—It was previously reported that a particular strain of *M. tuberculosis* forms a bright yellow pigment when grown in the presence of p-aminobenzoic acid (Paba). The color of the pigment fades after 10 to 21 days and the mass of bacilli grows darker. Compact masses of green-yellow, very shiny substances which are surrounded by groups of bacilli become visible under the microscope. The light-refraction of these yellow masses suggests that they may be crystalline, but no definite crystals could be identified. No pigment can be detected inside the bacilli. The present study deals with the conditions of this pigment formation. It has been established that magnesium is essential for the growth of *M. tuberculosis*. No pigment or very little pigment is formed when less than 0.05 per cent or more than 0.5 per cent magnesium sulfate is present; the optimal stimulating effect for pigment formation is reached at a concentration of 0.5 per cent. The pigment began to appear with concentrations of 100 gamma FeCl₃ per 100 ml.; the production of pigment was slight with 250 gamma per 100 ml., but increased to the usual amount with 500 gamma per 100 ml. When glycerol was replaced by glucose in Long's medium, the formation of yellow pigment was suppressed. If both glucose and glycerol were present, the pigment was formed as usual but to a lesser degree than in a medium which contained only glycerol. Studies made with buffered media show that glucose inhibits the appearance of the pigment through other mechanisms than the formation of acid. As glucose is a reducing agent, sodium ascorbate was added to determine whether it would have a similar effect. The formation of yellow pigment is completely suppressed. The optimal pH for the pigment formation lies near

pH 6; at pH 7.8 none is produced. The addition of riboflavin, pantothenic acid, thiamine and nicotinic acid did not change the appearance of yellow pigment formation. Sodium cyanide concentrations as low as 0.0005 M reduced the amount of pigment to as little as one-third of the usual amount. Young cultures acquire the ability to produce the yellow pigment after 3 to 4 days of growth but cultures cease to produce the pigment after 15 to 20 days. The same coloration is produced in the presence of procaine, other derivatives of Paba give no pigment, probably because their high bacteriostatic activity prevented the use of suitable concentrations. The pigment is practically insoluble in water, ether, chloroform and petroleum ether, but highly soluble in concentrated acetic acid and 88 per cent phenol. It is quickly decolorized in pyridine and when heated with acids or alkali. The yellow pigment contains oxidized NH_2 groups. Its chemical properties seem to show that it is, or contains, an unstable oxidation product of Paba and is formed from Paba by an enzyme which seems to be a specific oxidase.—*A Yellow Pigment Formed from p-Aminobenzoic Acid by Mycobacterium Tuberculosis Var. Hominis*, R. L. Mayer, J. Bact., September, 1944, 48: 337.—(F. G. Petrik)

Dextrorotatory Fatty Acids in Tubercle Bacilli.—By repeated fractionations of the methyl esters four different acids were isolated which differed in specific optical rotation and in molecular weight. The purified acids corresponded to the formulas $\text{C}_{24}\text{H}_{48}\text{O}_2$, $\text{C}_{25}\text{H}_{50}\text{O}_2$, $\text{C}_{26}\text{H}_{52}\text{O}_2$ and $\text{C}_{27}\text{H}_{54}\text{O}_2$. The properties of the acid having the formula $\text{C}_{26}\text{H}_{52}\text{O}_2$ agree with those reported for phthioic acid.—*Chemistry of the Lipids of Tubercle Bacilli. LXX. The Dextrorotatory Fatty Acids of the Acetone-Soluble Fat of Cell Residues from the Preparation of Tuberculin*, L. G. Ginger & R. J. Anderson, J. Biol. Chem., December, 1944, 156: 443.—(F. B. Seibert)

Methyl Groups in Branched Chain Fatty Acids.—Application of the Kuhn-Roth method for the determination of methyl groups at-

tached to carbon, on the acetone-soluble fat of tuberculin residues, indicated that these acids contain doubly branched chains.—*The Chemistry of the Lipids of Tubercle Bacilli. LXXI. The Determination of Terminal Methyl Groups in Branched Chain Fatty Acids*, L. G. Ginger, J. Biol. Chem., December, 1944, 156: 453.—(F. B. Seibert)

Mycocerosic Acid.—The normal fatty acids found in the wax isolated from tubercle bacilli residues from the preparation of the purified protein derivative PPD were palmitic, stearic, and hexacosanoic acids and an unsaturated acid probably oleic acid. The branched-chain fatty acids giving ether-soluble lead salts were separated into tuberculostearic acid, dextrorotatory acids analogous to phthioic acid, and a levorotatory acid, for which the name "mycocerosic" acid is proposed. This acid has been found to be a characteristic constituent of all the wax fractions of the human tubercle bacillus and it is obtained as a non-crystalline waxy solid, m.p. $27-28^\circ$, $[\alpha]_D$ in CHCl_3 -5 to -6° . Its composition corresponds to the formula $\text{C}_{30}\text{H}_{60}\text{O}_2$.—*The Chemistry of the Lipids of Tubercle Bacilli. LXXII. Fatty Acids Occurring in the Wax Prepared from Tuberculin Residues. Mycocerosic Acid*, L. G. Ginger & R. J. Anderson, J. Biol. Chem., January, 1945, 157: 203.—(F. B. Seibert)

Phthiocerol.—Evidence is presented which indicates that phthiocerol is a homogeneous substance and that its formula is either $\text{C}_{34}\text{H}_{67}(\text{OH})_2\text{OCH}_3$ or $\text{C}_{35}\text{H}_{69}(\text{OH})_2\text{OCH}_3$. Phthiocerane, the hydrocarbon prepared from phthiocerol by reduction of the iodo derivative, has been obtained in very pure form. It crystallizes in rosettes of fine needles and melts at 59 to 60° . Its formula is either $\text{C}_{34}\text{H}_{70}$ or $\text{C}_{35}\text{H}_{72}$. Its low melting point and high solubility would indicate that it has a branched chain structure. A new branched chain hydrocarbon 9,26-dimethyltetratricontane, $\text{CH}_3(\text{CH}_2)_7\text{CH}(\text{CH}_2)_{16}\text{CH}(\text{CH}_2)_7\text{CH}_3$ has been

$$\begin{array}{c} \text{CH}_3 \qquad \qquad \text{CH}_3 \\ | \qquad \qquad \qquad | \\ \text{CH}_2 \qquad \qquad \text{CH}_2 \end{array}$$

synthesized by electrolysis of tuberculostearic

acid and some of its properties have been determined.—*The Chemistry of the Lipids of Tubercle Bacilli*. LXXIII. *Studies on Phthiocerol*, L. G. Ginger & R. J. Anderson, *J. Biol. Chem.*, January, 1945, 157: 213.—(F. B. Seibert)

Carotin in Pulmonary Tuberculous Foci.—In lungs containing extensive caseous processes, particular yellow foci, constituted by accumulation of carotin pigment, may be encountered. The skin of patients with such pulmonary findings is slightly yellow, pseudoicteric. This pigment is contained in the alveolar endothelium in form of small drops or a diffuse discoloration. Whereas in other forms of hypercarotinemia, for example, in disturbances of the vitamin A metabolism, the cause is to be seen in a hepatic dysfunction; in the case of these pulmonary accumulations of carotin the author thinks that they are due to disturbances of respiration. Anoxia makes oxidation and destruction of the carotin impossible. Microscopically two forms of these carotinoid acino-lobular foci exist: (1) desquamative alveolitis, in which desquamated cells are filled with the pigment; (2) reticulofibrosis of the alveolar septa with proliferation of the alveolar endothelium toward the lumen. The insufficient gaseous exchange facilitates the precipitation of the pigment.—*Über eigenartige gelbe carotinoide Herde bei der Lungentuberkulose. Die pathogenetische Deutung der Hypercarotinaemie und der Dyspnoe ohne oder mit massiger Cyanose der Tuberkulosekranken*, C. Manzini, *Ztschr. f. Tuberk.*, 1942, 89: 21.—(G. Simmons)

Diasone in Guinea Pig Tuberculosis.—The effect of diasone was studied in guinea pigs with primary infection (Group A) and guinea pigs with reinfection tuberculosis (group B). Group A consisted of 18 animals which were infected by intramuscular injection of 0.1 mg. of human tubercle bacilli. Six animals served as controls (group 1), 6 were treated from the moment of inoculation (group 2), in 6 the treatment was started two weeks after the inoculation (group 3). The treatment consisted in oral administration of

150 mg. diasone, twice daily. The animals were killed two weeks, one month, one and a half months, two months, three months and four months after the inoculation. The control animals (group 1) showed rapidly developing tuberculosis of all organs with caseation; group 2 showed hardly any lesions in the organs, even four months after inoculation; in group 3, liver and spleen were affected two weeks after inoculation, but then the disease did not progress. Group B consisted of 17 guinea pigs which received a subcutaneous injection of 1 mg. BCG. One month later all animals reacted to intracutaneous tuberculin tests. One month after the injection of BCG the animals received intratracheally 0.1 mg. of human tubercle bacilli. Six animals served as controls (group 1), in 6 the treatment was started two weeks before the intratracheal infection (group 2), and in 5 the treatment was started two weeks after the intratracheal infection (group 3). The treatment was the same as in the primary infection group, and the animals were killed in the same intervals. Group 2 showed slower development of tuberculosis in lungs and other organs than the control group 1; in group 3 the diasone did not affect the development of the pulmonary lesions, but appeared to retard the development of tuberculosis in other organs. The average level of diasone in the blood was 3.0 mg. per cent, in the urine 81.0 mg. per cent. The only toxic effects were blood stasis in the spleen and hypertrophy of its reticuloendothelial tissue.—*Traitement de la tuberculose expérimentale du cobaye par la "diasone"*: 1. *Primo-infection*; 2. *Reinfection*, M. Giroux, *Laval méd.*, December, 1944, 9: 788.—(G. C. Leiner)

Sulfanilamide and Tubercle Bacilli.—Previous studies demonstrated that when a certain strain of *Mycobacterium tuberculosis* is cultured in Long's medium containing p-aminobenzoic acid (PABA) a yellow pigment is produced. The present study is concerned with the effect of sulfanilamide upon this same reaction. The organisms were grown in 18 mm. test tubes containing 10 ml. of Long's synthetic medium at 37°C. under the following sets of

conditions: (1) as control, and with the addition, before sterilization, of varying concentrations of (2) sulfanilamide, (3) PABA, (4) PABA plus sulfanilamide, (5) procaine and (6) procaine with sulfanilamide. The results show that the yellow pigment is produced regularly in the cultures containing PABA in concentrations of 1:750 and 1:5000. Sulfanilamide was capable in some cases of completely suppressing pigment formation in the tubes to which PABA had been added in dilutions of 1:2000 to 4000. On the other hand, a higher concentration of PABA, such as 1:1000, appreciably attenuated the inhibiting effect of sulfanilamide. To explain this inhibitory effect, the hypothesis of a direct chemical reaction between the oxidation products of PABA and sulfanilamide is propounded and discussed.—*The Influence of Sulfanilamide upon the Yellow Pigment Formed by Mycobacterium Tuberculosis from p-Aminobenzoic Acid*, R. L. Mayer, J. Bact., July, 1944, 48: 93.—(F. G. Petrik)

Chemotherapy with Amido-compounds of α -Furancarboxylic Acid.—The evaluation of a specific chemotherapeutic agent can be based up to a certain extent on the changes produced by it on the vitality of tubercle bacilli *in vivo*. The present study was based on the following method: the infectious agent was a tubercle bacillus of the human type, growing rapidly *in vitro*, and having conserved its virulence for guinea pigs, rabbits and mice. The experimental animal was the white mouse. The intravenous route of infection was used. The dose of infection was 0.5 mg. of a two-week old culture. The chemotherapeutic products were injected intramuscularly in oily suspension, the dose being somewhat below the maximal. Ten injections were given within two weeks. The evaluation of the results was as follows: suspensions of parenchymatous organs of 30 tuberculous white mice were cultured on Löwenstein's medium, 15 mice having received the chemotherapeutic agent and 15 serving as controls. The frequency of positive and negative cultures obtained from treated and control animals was compared.

The authors have studied the chemotherapeutic properties of amido-compounds other than the sulfonamides and not containing sulfur. The investigated substances were amido-compounds of α -furancarboxylic acid differing in the presence of the following groups: butyl, iso-butyl, heptyl, dimethyl, dipropyl, dibutyl, di-isobutyl, benzyl, -methyl-benzyl, propyl-benzyl, iso-butylbenzyl, dibenzyl, anilid. Of these investigated compounds the benzylamid of α -furancarboxylic acid showed the most pronounced activity in animals and appeared to be of low toxicity. Its administration in tuberculous mice resulted in a negative culture from their organs in 45 per cent of cases, whereas negative cultures with other amido-compounds were only found in 11 to 38 per cent of cases. These products were also studied in reference to their properties *in vitro* and also here the benzyl compound showed the most marked bactericidal and bacteriostatic effect.—*Investigations on the Chemotherapeutic Properties of Some Amido-compounds of α -Furancarboxylic Acid in Tuberculosis*, F. L. Chpanir & E. I. Chertkova, *Probl. tuberk.*, 1944, 4: 9.—(V. K. Leites)

Method of Testing Bacteriostatic Agents on Tubercle Bacilli.—Tubes containing 10 cc. of a synthetic medium were inoculated with dilutions of a suspension of tubercle bacilli and surface and subsurface growths recorded at seven days for the avirulent human strain 607 and at twenty-one days for the virulent strain H37Rv. The order of effectiveness of four compounds in inhibiting the growth of the avirulent strain was found to be: sulfathiazole, sulfadiazine, 4,4'-diaminodiphenylsulfone and sulfanilamide. For the virulent strain it was found to be: 4,4'-diaminodiphenylsulfone, sulfathiazole, sulfadiazine and sulfanilamide.—*An Improved Method for Testing the Bacteriostatic Agents Using Virulent Human Type Tubercle Bacilli*, G. P. Youmans, *Proc. Soc. Exper. Biol. & Med.*, October, 1944, 57: 119.—(F. B. Seibert)

Inhibitory Action of Tuberculo-carbohydrate and Phosphatide.—The carbohydrate

and phosphatide fractions of the tubercle bacillus exert a selective inhibitory action upon the endocellular enzyme, Cathepsin II, of tuberculous tissue. The carbohydrate caused no inhibition whatever upon normal liver cathepsin, while the phosphatide caused some inhibition but less than on the proteinases prepared from tuberculous tissues. This phenomenon may help to explain the cytotoxic action of tuberculin *in vitro* and also the failure of autolysis of caseous, tuberculous tissue.—*Inflammation. VII. Selective Inhibitory Action of Tuberculo-Carbohydrate and Phosphatide on Cellular Cathepsins from Tuberculous Tissues, C. Weiss & Nellie Halliday, Proc. Soc. Exper. Biol. & Med., December, 1944, 57: 299.*—(F. B. Seibert)

Bacteriostatic Property of Culture Filtrates.—The growth of the tubercle bacillus is inhibited by the filtrate of a liquid culture medium, which previously had been used for the culture of acid-fast tuberculosis and non-tuberculosis bacilli. On the other hand, the filtrate of a tuberculosis culture favors the growth of some acid-fast nontuberculosis bacilli.—*Presenza di proprietà attivanti o inibenti nei terreni liquidi che sono serviti allo sviluppo di bacilli acido-resistenti tubercolari e non-tubercolari, S. Savarino & D. Oricchio, Ann. Ist. Carlo Forlanini, 1943, 7: 408.*—(G. Simmons)

Tuberculostatic Action of Phenothiazine.—Phenothiazine dissolved in propylene glycol inhibited the growth of tubercle bacilli *in vitro* in high dilutions. In the presence of serum the bacteriostatic effect was diminished, but was still significant. Oxidized forms of phenothiazine showed moderate inhibition of growth. Other derivatives exhibited low tuberculostatic action.—*Tuberculostatic Action of Phenothiazine and Derivatives, B. L. Freedlander, Proc. Soc. Exper. Biol. & Med., October, 1944, 57: 106.*—(F. B. Seibert)

Antibacterial Effects on Tubercle Bacilli.—A number of organic substances, straight chain, cyclic and straight chain combined with

cyclic were added to Long's liquid synthetic medium to determine the approximate amount necessary to prevent the growth of the H37 strain of human tubercle bacilli. The amount of bacilli planted was 10^{-2} (about 10^6 bacilli). The method of dispersing and planting was that described by Drea with the exception that 10^{-1} per cent sodium hydroxide in distilled water was used to disperse the bacilli and prepare the first suspension of 1 mg./ml. The glassware was very clean and cotton stoppers were not used, the flasks were capped with loosely fitting aluminum caps or closely wrapped, thin aluminum foil. Growth always occurred first at the bottom of the liquid medium and, when the inhibiting agent was not too effective, extended to the surface of the medium. The appearance of the bottom growth was sufficient to justify a positive finding. Failure to observe a bottom growth was recorded as a complete inhibition of growth. The pronounced growth-inhibiting properties of C_{12} , C_{14} and C_{16} chain aliphatic bases are again emphasized. This is true for the simple compounds themselves, or when they are joined to or combined with radicals or other molecules such as benzene derivatives. The simpler benzene derivatives tested had the same relatively weak growth-preventing power of C_6 or C_7 straight chain acids. One exception was catechol with OH groups in the 1,2 positions which inhibited at 10^{-2} per cent concentrations. Sulfanilamide had its low antibacterial power increased by substitution into its molecule of either the pyrimidine or the thiazole nucleus. Morpholine, a saturated ring with 1 NH group and 1 O atom had no antibacterial power. It is suggested that rearrangements of certain molecules might result in increase of antibacterial powers. One of these is merthiolate, where the substitution of some other element such as Cd or Mn for Hg may be advantageous. Or, perhaps, the addition of a C_6 or longer aliphatic chain to the merthiolate molecule (modified or not, as before suggested) at the 4 position would be helpful. The possible applications for chemotherapeutic purposes are obvious since bacteriostatic powers are or may be quite as

important as bactericidal powers in such efforts.—*Antibacterial Effects of Various Organic Substances upon the H37 Strain of Human Tubercle Bacilli in a Simple Synthetic Medium*, W. F. Drea, *J. Bact.*, November, 1944, 48: 547.—(F. G. Petrik)

Inhibition of Mycobacterium by Streptothricin.—Streptothricin in amounts of 0.1 to 1.0 unit per ml. inhibited the growth of five mycobacterium strains on nutrient broth or Long's medium. It was found to be definitely bactericidal.—*In Vitro Inhibition of Mycobacteria by Streptothricin*, H. B. Woodruff & H. W. Foster, *Proc. Soc. Exper. Biol. & Med.*, October, 1944, 57: 88.—(F. B. Seibert)

Effect of Antibiotics on Tubercle Bacilli.—Numerous antibiotic substances had bacteriostatic activity for *Mycobacterium tuberculosis* which differed according to the species or even strains of the same species. Of these substances streptomycin was the most promising for practical utilization because of its relatively low toxicity. The addition of 200 to 300 units of streptomycin per 1 ml. of medium in which living cells of the tubercle bacilli were suspended, was sufficient to kill the cells within a period of a few days. Smaller amounts brought about death if a long period, ten days, of incubation was allowed.—*Effect of Streptomycin and other Antibiotic Substances upon Mycobacterium Tuberculosis and Related Organisms*, A. Schatz & S. A. Waksman, *Proc. Soc. Exper. Biol. & Med.*, November, 1944, 57: 244.—(F. B. Seibert)

Seasonal Tuberculin Allergy.—The study by Gomez and Epifanio (ibid. 1942, p. 269) on monthly and seasonal variations of tuberculin sensitivity is quoted and their findings of increased sensitivity early in summer and winter noted. The present authors tested 48,115 persons in Asuncion, Paraguay during 1941, 1942 and 1943. Persons were tested but once, and ages, sex and race are not given. Lowered sensitivity was found in autumn and spring of 1942, winter of 1941 and 1943. Heightened sensitivity was found in Novem-

ber and December of 1942 and December, 1943. A future paper will deal with some of the climatic factors, such as atmospheric pressure, humidity, temperature, that the authors think might be responsible for this change in allergy.—*La Allergia tuberculinica en relacion a las distintas epocas del año*, A. R. Gines & A. Wasmosi, *Hoja fisiol.*, June, 1944, 4: 93.—(J. S. Peterson)

Histamine and Tuberculin Desensitization.—The close relation existing between histamine and anaphylactic shock is well known and it suggests the rôle that histamine plays in allergic phenomena. Assuming the hypothesis that histamine is causative of the deleterious action on the tissue cells, it is only logical to try to counteract its action avoiding its liberation or neutralizing it (histaminase) or adopting the tissue (tachyphylaxis) so as not to show its action. This is what is called nonspecific desensitization or hyposensitization. Based on these facts, nonspecific histamine and specific tuberculin desensitization were practiced on a series of guinea pigs in order to compare the results and evaluate their action in the phenomena of the sensitization of the tuberculous inflammation. Sixty-six pigs were used for the experiment, divided into three series and were infected with 1.0 mg. of tubercle bacilli, subcutaneously in the first series, intratracheally in the second and intravenously in the third. Each series consisted of a control group, a second group treated with histamine and a third treated with tuberculin. In all the pigs the tuberculin sensitization was tested by the Mantoux technique. The chronologic evolution of the primary complex was analyzed in its two components, the primary focus and the regional lymphadenitis. In the series infected subcutaneously it was observed that in the groups desensitized with histamine and tuberculin there was evident retardation in the evolution of the nodule and ulceration of the lymph node involvement as compared with the control group. Observing the final development of the inoculation ulcer, it was noted that in those treated with tuberculin

the ulcer closed surrounding a caseous block; in those treated with histamine the ulcer healed with fibrosis, while in those of the control group the ulcer persisted until the death of the animal. The above characteristic also appeared in the general feature in the series infected intratracheally and intravenously, the lymphadenitis and caseation being smaller in the groups treated with histamine and tuberculin. The intravenous infection was characterized by a splenomegaly, which was smaller in the tuberculinized animals; the difference was noted principally in those treated with histamine, as compared with the control group. The study of the tuberculin sensitization curve showed the effect of tuberculin desensitization. The histamine treated animals remained sensitive to tuberculin but their reaction to the Mantoux test was stronger than in the controls. Tuberculin sensitization appeared soonest in the intratracheally infected group, later in the pigs cutaneously infected and latest in the intravenously infected pigs.—*Tuberculosis experimental y desensibilización con histamina y con tuberculina, Evolucion del complejo primario cutaneo y pulmonar, P. I. Elizalde, J. L. Monserrat & B. Anchezar, Rev. Asoc. méd. argent., March, 1944, 58: 125.*—(J. Badell)

Tuberculin Desensitization.—The authors studied the course of experimental tuberculosis in guinea pigs treated with crude tuberculin. Five groups of 5 animals weighing between 450 and 640 g. were used. Groups I and II received a sensitizing dose of 1 mg. of virulent tubercle bacilli in the groin. Four months later a second 1 mg. was injected. Group I was treated with tuberculin, group II was not. Groups III and IV served as controls for the first and second inoculations of tubercle bacilli. Group V was first treated with tuberculin and then infected. Daily doses of crude tuberculin were injected into the subcutaneous tissues of the abdomen. Starting with 1 mg. the dose was progressively increased to 2 g. by the third month. In group I treatments were begun twenty-eight days after the primary infection. In group V treatment

started three months before infection and continued until two weeks after. Each animal received a total of 58.8 g. of tuberculin within a treatment period of 108 days. The most notable observation during the treatment of group I was the early scarring of the tuberculous ulceration at the site of the primary inoculation. Healing was noted by the ninth day when only 56 mg. of tuberculin had been given. On the forty-fifth day of treatment the intracutaneous reaction was negative to 8 mg. of tuberculin. The second inoculation of bacilli into group I resulted in an early, shortened, attenuated reaction with little scar formation. The experiment was allowed to run until the death of all animals except 2 which were sacrificed. The weight curves showed considerable variations but no constant response to infection or treatment. At autopsy the animals in group I had no gross visceral lesions. In the inguinal lymph nodes there were small caseous centres. Group II animals, in contrast, had extensive lesions in the lungs, liver, spleen, and lymph nodes. Groups III and IV showed similar but more caseous lesions. Group V animals, tuberculin treated for three months preceding infection and for two weeks thereafter, showed disseminated fibrous or productive visceral and lymphatic lesions. The authors do not feel that their findings quite demonstrate the persistence of immunity after desensitization. They conclude (1) that desensitization is a fact, (2) that the treated animals early show evidence of increased immunity or heightened resistance, and (3) that the scarcity of macroscopic visceral lesions in the treated animals is related to desensitization and not to a direct chemical action of the tuberculin used. In the discussion which follows A. E. Bianchi affirms that the experiment proves that the treated animals have lost their hypersensitivity to tuberculin but not their allergy. Their prompt, shortened, and attenuated reaction to a second inoculation of tubercle bacilli is proof of the presence of allergy, a phenomenon which is distinct from both hypersensitivity and immunity.—*Tuberculosis experimental y desensibilización tuberculinica, P.*

Elizalde, O. Otoiz & B. Anchzar, *Rev. Asoc. méd. argent.*, April 15, 1944, 58: 165.—(R. Kegel)

Influence of Hormones on Tuberculin Reaction.—Hormones and tuberculin were injected at the same time into children with clinical and X-ray evidence of tuberculosis. Total extract of the thyroid and thyroxin enhanced, in the majority of cases, the skin reaction to tuberculin; extracts of the parathyroids and pituitrin usually caused a decrease in the intensity of the reaction. Adrenalin caused a slight decrease in about 50 per cent of the cases; hypophysin increased the reaction in some cases, whereas the thymus had no effect at all. An explanation of these phenomena is attempted: (1) these hormones act differently on the neurovegetative system and on the nerves which control the vessels; (2) in tuberculosis the vegetative system is altered in varying degrees.—*Azione degli ormoni sulla reazione alla tubercolina*, B. Edilio, *Ann. Ist. Maragliano*, 1941, 11: 111.—(G. Simmons)

Inhibition of Cathepsin by Tuberculin.—In view of experiments by Moen (showing that tissue cultures made from the spleens of animals infected with virulent tubercle bacilli were less active in their initial growth, when exposed to tuberculin, than were those taken from animals infected with an avirulent culture) and previous experiments by the authors (indicating a significant decrease in catheptic activity of the spleens of animals intravenously infected with tubercle bacilli—more so when virulent bovine than when bacilli of the R₁ strain were used) additional studies were undertaken in the hope of finding a catheptic inhibitor in tuberculin which might contribute to its cytotoxic action. PPD was used in the experiments. It was found that this substance produced a decrease of approximately 25 per cent in the activity of cathepsin II (an endocellular proteolytic enzyme presumably concerned in processes of cellular growth, repair and inflammation), and that this decrease was about the same

whether the cathepsin was obtained from the spleens of normal animals or from those infected with virulent or avirulent tubercle bacilli. Varying the concentration of PPD from 1×10^{-1} to 1×10^{-7} had no effect. Enzyme solutions prepared from other organs such as liver and kidney were similarly affected. PPD apparently acts as a general cathepsin inhibitor. Since phosphatide fractions have a similar effect, it is possible that these may be the inhibitors preventing caseous tuberculous tissue from undergoing autolysis.—*Studies on Inflammation. VI. Inhibitory Action of Tuberculin on Cathepsin*, C. Weiss & Nellie Halliday, *Arch. Path.*, April, 1944, 37: 272.—(D. G. Freiman)

Skin Reaction in Boeck's Sarcoid.—After the intracutaneous injection of a suspension of sarcoid tissue, obtained from a lymph node or a cutaneous nodule and prepared according to Frei's technique, the formation of a cutaneous nodule occurs at the site of the injection after one or several weeks, only in patients who have Boeck's sarcoid. This nodule persists for weeks or months and shows a structure identical with that of spontaneous sarcoid. Since the formation of such nodules could not be obtained with the same technique in normal individuals, it is considered a specific allergic skin reaction and the author is inclined to consider Boeck's sarcoid a separate disease entity.—*Eine neue spezifische Hautreaktion bei Boeckschem Sarkoid*, A. Kveim, *Nord. med.*, 1941, p. 169.—(G. Simmons)

Tuberculous Infection of Mice.—Mice were infected by exposure to air-borne suspensions of *M. tuberculosis*, bovis, introduced into a closed system. The author reports that the relatively high resistance possessed by mice to subcutaneous inoculation does not hold with the respiratory tract, since he found that comparatively small numbers of bacilli were capable of setting up infection, although the disease produced was not necessarily progressive. The organisms localized in the inter-aveolar tissues and evoked a reaction which bore a strong resemblance to that produced

in mice when injected either subcutaneously or intracutaneously with large doses. Bacilli multiply exceedingly freely and may spread throughout the pulmonary system. The tissue reaction is, however, mainly proliferative with the appearance of numerous "foam" and mononuclear cells. Caseation and necrosis were not seen. The figures, reported by the author, suggest that this species is almost as susceptible as the rabbit to infection by the respiratory route.—*Infection of Mice with Mycobact. Tuberculosis (Bovis) by the Respiratory Route*, R. E. Glover, *Brit. J. Exper. Path.*, October, 1944, 25: 141.—(H. J. Henderson)

Pulmonary and Extrapulmonary Tuberculosis.—At the conclusion of the period of generalization of tuberculosis, there is a humoral immunity which permits the development of tuberculosis only in isolated organs. In about one-fourth to one-third of the tuberculous patients no humoral immunity develops or it develops only slowly, so that for a long time metastatic spread remains possible and tuberculosis of multiple organs may result. Generally the single *poussées* of such a tuberculosis are benign, but due to the prolongation of the period of generalization the danger of a miliary tuberculosis or of a meningitis remains. The tendency to such forms of tuberculosis appears to be based on constitutional and hereditary properties. Since such patients appear to be sensitive toward superinfection, they should be separated from cases of open tuberculosis. Desensitization with tuberculin may decrease the allergic sensitivity and may shorten the period of generalization.—*Über die isolierte und multiple Organtuberkulose und über das Verhältnis der pulmonalen zur extrapulmonalen Tuberkulose*, F. Ickert, *Klin. Wchnschr.*, 1942, 1: 518.—(G. Simmons)

Extrapulmonary Tuberculosis.—Three cases of extrapulmonary tuberculosis without manifest pulmonary lesions are presented. Two of the cases present acute symptoms of rheumatism with formation of abscesses which were opened and developed tuberculous sinuses; one of the 5 cases had also Pott's disease. The

third case had painful enlargement of the lymph nodes of the right side of the neck, supraclavicular area and of the right axilla. None of the cases presented any symptoms of pulmonary tuberculosis on auscultation. The Mantoux test was positive in all 3 cases. The sputa were negative for tubercle bacilli; the serological tests were negative; fluoroscopic examinations and X-ray films of the chest failed to reveal any parenchymatous lesion, except slight enlargement of both hila and blood vessel markings in one case. Hemograms were within normal limits in 2 cases, but biopsies were performed and the ulcerative processes were tuberculous in all 3 cases. The cases were three of the most varied forms of extrathoracic localization in the bone, skin and lymph nodes. The author states that extrapulmonary tuberculous lesions are more frequent than it is generally believed. These tuberculous or pseudotuberculous extrapulmonary lesions are often not recognized.—*Algunos casos interesantes de tuberculosis extrapulmonares, sin lesiones pulmonares evidentes o evolutivas*, T. Garcia Pérez, *Rev. de tuberc. d. Cuba*, October-December, 1943, 7: 510.—(J. Badell)

Treatment of Tuberculous Bronchitis.—In pulmonary tuberculosis the prognosis is considerably worse if it is associated with tuberculosis of the bronchi. The effectiveness of collapse therapy depends largely on this complication. The obstruction of a bronchus can occasionally have a favorable effect on tuberculosis of the pulmonary parenchyma. The resulting atelectasis may cause closure of a cavity and lead to sclerosis of the lesions. The development of bacilli is impeded by the lack of air. On the other hand, an unfavorable effect is produced if the bronchitis is of the progressive type. The apneumotosis causes progression of the pulmonary lesions, secondary infection, empyema and even bronchopleural fistula. There is still much difference of opinion as to the efficiency of collapse therapy in these cases. Some believe that pneumothorax has a favorable effect even on tuberculous lesions of the trachea and the

large bronchi. Others believe that a pneumothorax will aggravate the condition. Alexander is of the opinion that collapse therapy, especially thoracoplasty, has no influence whatever on tuberculous ulcerations of the trachea and the bronchi. The authors believe that pneumothorax has a decidedly beneficial effect on the pulmonary lesions even if they are complicated by bronchial ulcerations. They base their opinion on the fact that they had a large number of good results in cavernous types of tuberculosis with ulcerations, endobronchitis, or even ulcerative stenosis of the bronchi, and that the discontinuation of pneumothorax has always been followed by a disastrous result. But the results are always much inferior to cases not complicated by bronchial ulcerations. Ornstein and Epstein use pneumothorax even in all cases of tuberculous bronchitis without involvement of the parenchyma to prevent pulmonary spread. On the other hand, a pneumothorax may transform a partial obstruction into a complete occlusion. Phrenemphraxis is more dangerous than pneumothorax. Thoracoplasty is considered the method of choice. Each case must be considered individually after bronchoscopy and after a pneumothorax has been tried. If the endobronchitis is of congestive or edematous nature, the treatment will be established as if no complications existed. In all other cases, the bronchial lesion must be treated locally by application of silver nitrate, before the commencement of collapse therapy. In their own clinic the authors treated cases having minimal bronchial lesions with pneumothorax. The more advanced cases were treated with thoracoplasty and also, if possible, those with stenosis of a bronchus. When this is not feasible and the lesions are localized in the middle or inferior lobe, lobectomy is done, provided the bronchus is not affected orad to its surgical division. Phrenicotomy is considered contraindicated in all cases. Bilateral bronchial ulcerations are generally past any surgical intervention. If a lobular atelectasis exists in a patient previously treated with pneumothorax, a thoracoplasty is done, but the collapse of the lung by air is

maintained during and after the operation to avoid reëxpansion of the unaerated lobe with its often disastrous results.—*El tratamiento de la tuberculosis pulmonar con bronquitis tuberculosa asociada*, R. F. Vaccarezza & A. E. Bence, *Prensa méd. argent.*, October 4, 1944, 31: 1971.—(W. Swienty)

Tuberculosis of Trachea and Bronchi.—The author reports his autopsy observations on 100 patients dying of pulmonary tuberculosis (age and sex not stated). On gross examination ulcerative lesions of the trachea were found in 20 patients. Lesions of some segment of the primary or lobular bronchi were found in 25 patients. Counting both tracheal and bronchial lesions a total of 32 patients was affected. One patient showed an almost complete stenosis of the bronchus to the right upper lobe. In another patient a caseous lymph node had perforated the wall of the right upper lobe bronchus. Histological studies showed tuberculous lesions of the trachea in 28 and of the bronchi in 70 patients. Macroscopic tuberculous laryngeal lesions were found in 54 of 99 postmortem examinations. Of the 54 patients with laryngeal tuberculosis, 30 per cent showed macroscopic tracheal lesions and 39 per cent bronchial lesions while of the 45 patients with normal larynges only 9 per cent had tracheal lesions and 9 per cent bronchial lesions. The author notes the frequency of extensive caseation of the peribronchial lymph nodes and of fresh tuberculous caseous bronchitis.—*Lesiones tuberculosas de la traquea y de los bronquios encontradas en cien autopsias de tuberculosos*, J. A. Perez, *Rev. de tuberc. d. Uruguay*, No. 1, 1944, 12: 1.—(R. Kegel)

Patent Bronchi.—The use of methylene blue instead of lipiodol for the determination of the patency of a bronchus leading into a cavity is advocated. From an analysis of the period of time it took the patient to bring the dye up in the sputum and of the position of the patient an idea of the patency and the position of the draining bronchus can be obtained.—*Beitrag zur Darstellung des ableitenden Bronchus der*

tuberkulösen Kaverne, J. Obstmayer, Beitr. z. Klin. d. Tuberk., 1942, 97: 684.—(G. Simmons)

Tuberculous Tracheobronchitis.—Bronchoscopy was performed in all cases of pulmonary tuberculosis as a routine examination, except when definitely contraindicated. In 1,200 cases no serious complications were observed. Congestion and edema of the bronchial mucosa were common findings; their interpretation, however, is difficult, unless they are associated with definite tuberculous lesions, or their evolution on successive observation proves to be toward typical submucous infiltration or ulcerogranulomatous lesions. Bronchial stenosis in pulmonary tuberculosis can be caused by endobronchial changes (congestion, edema, ulcero-granulomatous or fibrostenotic lesions), or by tracheobronchial or hilar adenopathy. While the first type of bronchostenosis occurs more often in adults, the latter is more frequent in children. The bronchoscopic examination discloses certain data concerning the flaccidity or the rigidity of the bronchial wall, and also certain kinetic changes of the bronchial tree in relation to the status of the other components of the respiratory tract. The following bronchoscopic findings were recorded in the presence of therapeutic pneumothorax: the normal upwards and downwards dislocation of the carina, produced by the act of respiration, shows a deviation toward the collapsed side during the downward movement; the greater bronchi appear shortened, but not collapsed, and follow the respiratory movements; the lobar bronchi are dislocated and their respiratory excursion is reduced; the intralobar branches may remain normal in the healthy lobuli, while they appear condensed in the collapsed lobuli. The diagnosis of tuberculous tracheobronchitis is based on the clinical syndrome and on the bronchoscopic findings, confirmed by the presence of tubercle bacilli in the sputum. Biopsy is mostly contraindicated, particularly in non-ulcerative lesions. The treatment of endobronchial tuberculosis, in absence of clinically evident parenchymatous involvement, is directed to calm the symptoms, to cure the

lesions and to prevent stenosis. Gold therapy and vitamin C can be given, besides general measures and symptomatic medication. Silver nitrate in 20 per cent solution, used every fifteen days, appears to be the most rational local therapy. Bronchoscopic dilatation, followed by aspiration of the secretions, can be attempted in localized annular stenosis after the disappearance of all symptoms of activity. This method is, however, risky and the results are uncertain. The suppurative complications beyond the blocked bronchus are treated by endoscopic dilation and aspiration of the pus and by local sulfanilamide therapy. The treatment of endobronchial tuberculosis associated with active and extensive primary or postprimary lesions has to be more conservative than that of the apparently primary endobronchial disease. The presence of endobronchial disease impairs the prognosis of pulmonary tuberculosis and complicates also the various collapse-therapeutic measures. The available statistical data are still contradictory in this respect. When the involvement is limited to the bronchus of the diseased lobe, pneumothorax is still possible, especially if complemented by rational bronchoscopic treatment. In the presence of more extensive bronchial tuberculosis, surgical treatment can only be considered after the bronchial lesions have become at least quiescent. Thoracoplasty sometimes followed by pneumonectomy, or lobectomy or pneumonectomy not preceded by thoracoplasty, can be performed successfully in a certain number of cases. The revision of a series of ineffective pneumothoraces has shown that bronchial lesions are a frequent cause of the failure of the collapse therapy. The bronchial tree has shown little changes in those cases where a pachipleuritis was the cause of the failure of the lung to reexpand. There were more important bronchoscopic findings in lungs showing an extensive fibrosis. It appears evident that a bronchoscopic examination must precede every collapse-therapeutic procedure.—*Traqueobronchitis tuberculosa, R. A. Piaggio Blanco & J. C. Dighiero, Rev. de tuberc. d. Uruguay, No. 5, 1943, 11: 313.—(L. Molnar)*

Closure of Bronchocutaneous Fistula with Muscle Flap.—A bronchocutaneous fistula will often not close after drainage has been discontinued, whereupon it is necessary to close it by surgery. For this purpose Aguilar uses a muscle flap in cases where drainage of a pulmonary abscess has resulted in a bronchial fistula of moderate size. It should be made certain that the local inflammation has subsided, that there is no bronchiectasis of considerable size and no residual empyema cavity. The coexistence of tuberculosis does not change the operative outlook, but should be known in advance. The technique consists of a combination of resection of the fistula tract and the filling-in of the resulting cavity with a pediculated muscular flap. This flap should be sufficiently large to close not only the tract but also all possibly existing intrapulmonary residual cavities. The muscle must be cut in the direction of the fibres and as much fat as possible should be adherent to it, as this contributes to better nourishment of the flap. Under local anesthesia the fistula is removed by circular incision. A muscle flap is mobilized after careful hemostasis. This flap is introduced and after it has been made certain that all of the scar tissue has been removed and the healthy lung tissue laid free, the flap is introduced into the resulting funnel and secured there with separate stitches. A rubber drain is inserted and local compression maintained for five to seven days.—*Cirugia toracica, Fistulas bronchocutaneas, cierre con colgajo muscular, D. Aguilar, Prensa méd. argent., August 9, 1944, 31: 1469.*—(W. Swienty)

Diagnosis of Hilar Adenopathy.—The increasing frequency of primary tuberculosis in the adult has made the radiological diagnosis of the tracheobronchial adenopathy a matter of current importance. As a matter of fact, when no reference is had to tuberculin conversion, the presence of mediastinal lymph node enlargement indicates, with few exceptions, a diagnosis of primary tuberculosis. The radiological diagnosis of this hilar adenopathy is nevertheless difficult. Many abnor-

mal hilar shadows are diagnosed as lymph node enlargement. Lateral radiography and tomography are thus of great value in those cases, as they permit the elements of the radiological hilum to be distinguished from each other. Thus the pulmonary processes located on the borders of the lung and particularly on the apex of the inferior lobe can be diagnosed. Very often the enlarged hilar image corresponds to an abnormality of the pulmonary artery. It is emphasized that sometimes the pulmonary artery in the left hilum is not mostly covered by the edge of the pericardium, the result of which is an enlarged radiological image, which commonly is interpreted as hilar adenopathy. With these restrictions the diagnosis of a tracheobronchial tuberculous adenopathy has been made only twice in 1,389 cases, one of which was confirmed at autopsy. The study of the lateral radiogram, where the lymph node enlargement is projected behind and under the tracheal bifurcation, or before and/or behind the trachea, is emphasized. The pulmonary artery is projected in front of the tracheal bifurcation.—*Algunas consideraciones sobre el diagnóstico radiológico de adenopatía traqueo-bronquica tuberculosa en el adulto, B. Juricic, G. Gonzalez & H. Duran, Ap. respir. y tuberc. (Chile), April-June, 1944, 9: 103.*—(H. Behm)

Bilateral Pleurisy and Phlebitis.—Within a period of four months a 28 year old male whose father had pulmonary tuberculosis with cavitation developed successively a parotitis, a unilateral orchitis, a serofibrinous effusion in the left pleural cavity, a pleuritis on the right side (both processes initiated by a paralytic ileus) and finally a phlebitis of both legs. The pleural fluid was not examined but the author believes the pleurisy due to tuberculosis. He feels that tuberculosis is the probable cause of the phlebitis also. No direct evidence is adduced.—*Pleuresia sero-fibrinosa, cortico-pleuritis, y flebitis sobre su etiogenia, H. E. Osacar, Rev. méd. d. Hosp. Ital. d. La Plata, June, 1944, 1: 127.*—(R. Kegel)

Tuberculous Pleurisy.—Serofibrinous pleural effusion occurred in 50 cases of the post-primary stage of childhood tuberculosis between the ages from 7 to 12 years. The complication developed more frequently in spring than in any other season and involved both the homolateral and contralateral hemithorax. Fifty-two per cent occurred during the period of sanatorium treatment. Rest, therefore, seems to be of little preventive importance. Pleural effusion like other toxic manifestations is probably inevitable and depends on constitutional and immunobiological factors. In 9 cases the course was afebrile, in 35 cases fever lasted from 7 to 20 days, in 4 from 20 days to 2 months and in 2 from 7 months and over. The immediate prognosis depends much on the course during the first month, on fever, sedimentation rate and radiological signs. Ninety-eight per cent of the cases of so-called allergic serofibrinous pleurisy healed. In cases of an established pleural tuberculosis the prognosis is grave: 2 of 5 children with this complication died.—*Consideraciones sobre pleuresia serofibrinosa tuberculosa y su pronostico*, R. Matte & E. Saldias, *Rev. chilena de pediat.*, August, 1944, 15: 638.—(F. G. Kautz)

Therapeutic Cutaneous Emphysema.—A cutaneous emphysema was artificially produced in order to obtain a nonspecific stimulus over a diseased organ. One hundred to 400 cc. of air were thus introduced subcutaneously. Four cases are reported. This kind of treatment was used in cases of pleurisy with and without effusion. In the majority of cases the results were "surprising." Improvement was obtained in several cases of persistent disease of the colon. No objective results were obtained in peptic ulcers. In 3 cases of chronic arthritis the results were "satisfactory." Bronchial asthma was not benefited.—*Das artifizielle Hautemphysem zur Reiztherapie*, R. Boller, *Klin. Wchnschr.*, 1942, 1: 587.—(G. Simmons)

Primary Tuberculosis of Palate.—The authors present a case of tuberculous ulceration

of the gums which is considered to be a primary complex. Biopsy revealed giant cells of the Langhans type and epithelioid cells. Aspiration of the submaxillary lymph node revealed caseation and numerous tubercle bacilli. This condition is very rare. This was a primary infection in a 24 year old patient. She had been treated previously for infection of the gum and syphilis without success. The Mantoux test, applied late in the disease, was strongly positive. Following the test the patient had a general reaction with fever and a local increase of the ulcer. The cervical lymph nodes broke down. Subsequently, she was treated for her tuberculosis. The lesions of the gum and the node disappeared, leaving only slight scars. There was no evidence of any tuberculosis of the lungs.—*Tuberculosis primitiva del paladar*, V. J. Bertola & A. Ferraris, *Prensa méd. argent.*, November 1, 1944, 31: 2219.—(W. Swienty)

Tuberculosis of Stomach.—Ulcerative tuberculosis of the stomach is infrequent; the number of cases hitherto reported approximates 200, though Chaffin (1937), eliminating doubtful cases out of 211 published, only considered 51. Eustermann and Balfour (1938) recorded only 58 cases. Sometimes the ulcer is a fortuitous autopsy finding and in some other instances its presence is manifested by hematemesis or gastric perforation. Both hematemesis and perforation occurred in the present case, a 22 year old soldier who had pulmonary and pleuroperitoneal tuberculosis with a positive sputum and a negative Mantoux test. The main findings at the post-mortem examination were two esophageal ulcers, one of them perforated, opening into a fistulous tract from a softened caseous periesophageal lymph node. In the stomach there was a great amount of liquid and clotted, undigested blood; a perforated ulcer in the neighborhood of the cardia, several other gastric ulcers were scattered throughout the mucosa. There was a generalized intestinal tuberculosis. Nodular lesions, predominantly exudative, were found in all the layers of the stomach. Blood vessels participated in the

process, presenting lesions of stenotic endoarteritis, some of them with parietal or occlusive thrombi. The lymphatic vessels contained caseous thrombi and stenotic productive lymphangitis. Two fundamental mechanisms have been invoked in the production of ulcerative tuberculosis of the stomach: hematogenous dissemination (Pripier, Arloing) and lymphatic spread (Chiari, Rosset, Grossmann). Attention is called to the fact that there was a predominance of lesions due to the hematogenous spread in this case.—

Ulceras tuberculosas multiples del estomago, una de ellas perforada, D. Fernandez Luna & R. I. Latienda, Rev. Assoc. méd. argent., January-February, 1944, 58: 30.—(J. Badell)

Tuberculosis of Stomach.—Gastric tuberculosis is rare—0.11 per cent of all tuberculosis cases. Only 25 cases were published so far in the Japanese literature. In the majority of cases gastric tuberculosis is a secondary infection caused by swallowing of infected sputum. Thirteen of the cases reported were considered cases of primary gastric tuberculosis. Gastric tuberculosis may assume one of three forms: (1) ulcerative, (2) hypertrophic, (3) atrophic. The case reported, diagnosed clinically as a benign pyloric stricture and operated on, showed multiple ulcers in the pyloric region with an extensive gastritis. The perigastric lymph nodes were tuberculous. In this case the gastric tuberculosis was obviously secondary to pulmonary tuberculosis, since the patient had bilateral apical disease and had been under treatment before for his pulmonary condition as well as for a tuberculous lymphadenitis of the neck.—*Über einen operierten Fall von Magentuberkulose, Y. Kabuki, Deutsche Ztschr. f. Chir., 1942, 355: 309.—(G. Simmons)*

Tuberculosis of Stomach and Cancer.—A case of gastric tuberculosis with secondary carcinomatous degeneration is reported. Clinically the diagnosis of carcinoma was made and the patient was operated on (Billroth-I-Kocher). The operation was successful. The final diagnosis was made microscop-

ically. Only 24 cases of gastric tuberculosis and carcinoma have been reported in the literature so far.—*Ein Fall von Magentuberkulose mit sekundärer krebsiger Wucherung, F. Adamesik & J. Erdély, Chirurg., 1942, 14: 304.—(G. Simmons)*

Duodenal Tuberculous Ulcer.—In 600 autopsies of cases of tuberculosis, a total of 21 intestinal ulcers (3.5 per cent) were found; among them 4 were peptic ulcers, one case of hemorrhagic erosions, 13 lenticular ulcerations and 3 nummular caseous ulcers. Of these 3 cases the last one was a 30 year old male, with advanced pulmonary and intestinal tuberculosis. There was a periduodenitis; no ulcer was seen. The patient died a year later and at autopsy the main features were: generalized mesenteric caseous adenopathy; near Vater's ampulla was a crater-like ulceration and tubercles in the duodenal wall, corresponding to lymph nodes, and engorged lymph vessels emptying in the anterior duodenopancreatic lymph nodes. There were scattered ulcers in different parts of the intestinal tract and at the splenic flexure a small one was perforated. Histological sections of the ulcer revealed tuberculous lymphangitis and softened caseous tubercles teeming with tubercle bacilli. In reviewing the pathogenesis of the ulcer, the retrograde lymphatic way is the most acceptable way to explain it, considering the existence of a caseous tuberculous adenopathy of the superior mesenteric lymph nodes, and the fact that the pancreaticoduodenal lymph nodes are tributary of the mesenteric nodes. There was probably a stasis in the lymph channels of the second and third portions of the duodenum and the infection of their contents caused the tuberculous lymphangitis and the ascending infection of all the parietal portion of the duodenum.—

Ulceras tuberculosa caseosa de la segunda porcion del duodeno, D. Fernandez Luna & F. Cruz Arnedo, Rev. Assoc. méd. argent., January-February, 1944, 58: 17.—(J. Badell)

Enterogenous Tuberculosis.—X-ray films of the chest, the abdomen and the neck were

made in 155 children with a positive skin reaction. In 70 cases (45 per cent) X-ray evidence of tuberculosis was found. And, surprisingly, in 31 cases there was evidence of healed tuberculosis in the abdominal lymph nodes. Clinically the diagnosis of tuberculosis of the abdominal lymph nodes is extremely difficult and a diagnosis can only be made after the nodes have become calcified. In one-fourth of the cases with tuberculosis of the lymph nodes there were signs suggestive of intestinal tuberculosis. This condition is particularly frequent among children of the age group 1 to 3. Not infrequently a fatal meningitis originates from an enterogenous primary complex (10 per cent). The author considers, therefore, enterogenous tuberculosis infection in children a great danger.—*Die Bedeutung der enterogenen Tuberkuloseinfektion im Kindesalter*, O. Cammann, *Med. Klin.*, 1942, 11: 673.—(G. Simmons)

✓ **Tuberculous Peritonitis.**—Of 21 cases of tuberculous peritonitis observed within a period of 6 years, 17 occurred among ward patients and 4 among the private patients of a General Hospital. The majority of the patients was between the ages from 19 to 30 years; one child of 12 years, one woman of 43 years and one woman of over 80 fell outside of this age group. The race distribution was 3 whites, 3 Indians and 15 Mestizoes. The lesion was diagnosed in 8 cases as ascites and in 13 cases as a fibroplastic peritonitis. During the hospital stay no other active tuberculous focus could be discovered. The symptomatology of tuberculous peritonitis is protean and often simulates appendicitis, salpingitis, cholecystitis and abdominal tumors. The preoperative diagnosis in these cases was correct in 70 per cent, definitely established in 45 per cent and strongly suggestive in 25 per cent. Treatment consisted in laparotomy. The author feels that tuberculous peritonitis should be kept in mind whenever one of the common abdominal lesions presents a bizarre course. The clinical diagnosis can often be made with accuracy. A diffuse median contraction of the abdominal wall

without any further definite point tenderness and without abdominal distention proved to be a persistent and reliable diagnostic sign.—*Peritonitis tuberculosa*, E. St. Loup, *Gaz. Med. Quirurg. de Bolivia*, May, 1943, 1: 9.—(F. G. Kautz)

✓ **Pyelogram in Renal Tuberculosis.**—In early tuberculosis of the kidney the three main diagnostic findings, namely, tubercle bacilli in the urine, pyuria and renal dysfunction, may be absent. Even the presence of tubercle bacilli in the urine is not of absolute diagnostic value, because the problem as to whether bacilluria cannot be present despite a perfectly healthy kidney is not yet solved. The author is of the opinion that the pyelogram is an important aid in the diagnosis of early kidney tuberculosis, and he distinguishes three early stages: (1) small, marginal foci of destruction in the kidney parenchyma adjacent to the pelvis; (2) small caseous foci or cavities in the medulla, communicating with the pelvis; (3) caseous foci or cavities not communicating with the pelvis. In the first and in the last case the findings are of no additional diagnostic value, because similar changes may occur in nonspecific conditions of the kidney. In the second case, however, the findings are said to be so typical, that they alone are sufficient for a diagnosis.—*Die Früherkennung der Nierentuberkulose im Pyelogramm*, C. H. Schroeder, *Ztschr. f. urol. Chir. u. Gynäk.*, 1942, 46: 274.—(G. Simmons)

Tuberculosis and Hydatid Cyst of Kidney.—One instance of this rare combination is reported. The patient was a 38 year old mother of six healthy children. The present illness began with an acute attack of renal colic three years previously. The patient was well until six months before admission when right-sided pleuritic pain followed by a dry cough, dyspnea on exertion, anorexia, asthenia and night sweats appeared. She lost 44 pounds. The physical examination revealed signs of a pleural effusion. In the right upper abdominal quadrant there was an orange-sized, painful mass apparent on deep palpation. A

thoracocentesis yielded 800 cc. of yellowish green purulent fluid. A guinea pig inoculated with the fluid died of intercurrent infection. Six weeks later profuse pyuria occurred and the abdominal tumor disappeared. Retrograde pyelography outlined a cyst in the superior pole of the right kidney. Casoni's reaction was strongly positive. An operation was attempted, during which the patient died. Autopsy revealed a tuberculous pleuritis and a fibrotic tuberculosis of the right lung. In the upper pole of the right kidney there was a 12 x 5 x 3 cm. cyst with calcified walls. The cyst was firmly adherent to the diaphragm but no communication between pleura and cyst was found. Microscopic examination showed an exudative tuberculosis of the kidney.—*Tuberculosis y quiste hidático asociados en riñon derecho*, A. Cisneros, J. Parisi & G. Cahn, *Rev. Asoc. méd. argent.*, July 30, 1944, 58: 584.—(R. Kegel)

Tuberculous Aneurysm.—A 72 year old white woman was admitted to the hospital with complaints of abdominal pain, fever, chills and weight loss. On physical examination there was a large, moderately tender, firm, slightly movable mass in the right lateral portion of the abdomen. Death occurred under the signs of blood loss. At autopsy a large perirenal hematoma was found in the right paravertebral gutter. Attached to the mediocephalad vertebral surface of the hematoma was a firm brownish purple dumb-bell-shaped mass, measuring 8 by 6 cm., which encircled the anterior margin of the abdominal aorta between the diaphragm and the celiac axis. In the right ventral aspect of the aorta there was an oblong rent, 1 cm. in diameter. The peritoneal portion of the dumb-bell-shaped sac consisted of periaortic connective tissue. There was a laceration from this sac into the perirenal space. On microscopic examination there was necrosis of the media at the mouth of the aneurysm. The adventitia was thickened and showed Langhans cells, lymphocytes and plasma cells. Acid-fast bacilli were found between the elastic tissue fibres of the aorta. There was tuberculosis of

lungs, liver, spleen, kidneys, adrenals. It is believed that acid-fast bacilli were disseminated from a right hilar lymph node through the blood stream to the media of the aorta.—*Tuberculous Aneurysm of the Abdominal Aorta*, J. N. Owens, Jr. & A. D. Bass, *Arch. Int. Med.*, December, 1944, 74: 413.—(G. C. Leiner)

Pericardium in Tuberculous Patients.—In 22 per cent of 45 patients who died of pulmonary tuberculosis microscopic examination of the parietal pleura revealed the presence of tuberculous changes. In almost all cases specific cellular reactions were found in addition.—*Ricerche istologiche sulla membrana pericardica parietale di soggetti deceduti per tubercolosi polmonare*, I. Rocchio, *Ann. Ist. Carlo Forlanini*, 1943, 7: 73.—(G. Simmons)

Meningitis and Tuberculosis of Uterus.—The present report deals with a 25 year old female who was admitted to the hospital in a state of stupor, delirium and mental hallucinations. A diagnosis of tuberculous meningitis was established; the patient died eleven days after her admission. The main features revealed by the postmortem examination were caseous tuberculosis of the uterus, fallopian tubes and ovaries, left tuberculous pleuritis, miliary lesions in the right upper lobe, tuberculous perihepatitis and tuberculous meningitis. The extensive and far-advanced salpingo-uterine lesions prove that they preceded the meningeal lesions; the other seedings in pleura, lung and liver reveal successive localizations. It is very infrequent to see primary or secondary tuberculosis of the uterus ending in tuberculous meningitis.—*Tuberculosis caseosa del utero: Meningitis terminal tuberculosa*, I. R. Steinber & C. A. Crivellari, *Rev. Asoc. méd. argent.*, January-February, 1944, 58: 25.—(J. Badell)

✓ **Tuberculosis of Eye.**—In honor of Robert Koch the authors celebrate his one hundredth birthday anniversary with a review of his discoveries and their influence on ophthalmology. In his famous experiments he succeeded

in causing pulmonary and generalized tuberculosis by inoculation of tubercle bacilli into the anterior chamber of the eyes of rabbits. After inoculation in the conjunctiva, changes occur in the preauricular lymph node which are easy to observe. Twenty cases of primary tuberculous conjunctivitis without lymph node changes have been observed, the last by MacKenzie. The prognosis of primary infection of the conjunctiva is always guarded. The authors saw one case in which the lungs were infected. Tuberculous infection of the cornea has to be considered as reinfection. It has not been possible to cause tuberculous lesions in the deep structures of the eye by direct spread. In 74.1 per cent of a series (70 cases) of phlyctenular conjunctivitis published by Ruza and others in 1942, tubercle bacilli were found in the gastric contents and 58.8 per cent had pulmonary lesions. All cases but one had a positive patch test. As phlyctenulae can be produced by all types of allergic substances, it can be said that the phlyctenula is a nonspecific reaction. In warm countries it is known to be a complication of catarrhal conjunctivitis. Intraocular tuberculosis has to be considered as a localization by hematogenous spread. Primary tuberculosis in the eye is very rare. In the uvea it is due to suprainfection after allergization. The experiments of LaGrange and Stock (injection of bacilli into the carotid artery and auricular vein of the rabbit) are recalled. The relative rareness of tuberculosis of the eye in the far advanced stage of pulmonary tuberculosis has been explained by Ranke who found that there is little tendency to hematogenous spread in these cases. The most frequent forms of tuberculosis of the eye are iritis and iridocyclitis. These are allergic reactions but not always of specific etiology. Two forms of iritis may be distinguished, the exudative and the proliferative. The former is due to allergic reaction of the tissues and the latter due to the presence of the bacillus itself. It seems proved that local infection of the eye may persist without skin allergy. Phlyctenular conjunctivitis gives the highest percentage of positive skin tests. At the Santa Lucia

Hospital the authors observed that intraocular tuberculous lesions are at least as frequent as phlyctenular conjunctivitis. In miliary tuberculosis of the eye, anergy is frequent. It is difficult to decide whether keratitis and scleritis are allergic reactions or not.—*Tuberculosis Ocular*, E. Adroque & B. G. Tiscornia, *Rev. Asoc. méd. argent.*, December 15, 1943, 523: 1053.—(W. Swienty)

Tuberculosis of Eye.—A brief historical sketch of general tuberculosis and of tuberculosis of the eye is presented. The first who called attention to ocular tuberculosis was Antoine Maitre-Jan (born 1650). The invention of the ophthalmoscope by Helmholtz is discussed and a short biography of Robert Koch is given. From a review of the literature the author draws the following conclusions: The relation of ocular tuberculosis to tuberculosis of other organs, particularly the pulmonary form, has not been definitely established. A positive tuberculin reaction and a favorable response to tuberculin injections are no proof of the diagnosis. The eye appears to possess an immunity in active pulmonary tuberculosis. Phlyctenular keratoconjunctivitis is not usually of tuberculous origin. Tuberculous lesions of the eye are not nearly as common as they are generally supposed. Uveal tuberculosis is not necessarily secondary to tuberculosis elsewhere in the body. The nature of an infection in the anterior segment of the eye should always be determined in the laboratory.—*Ocular Tuberculosis: Its Relation to General Tuberculosis*, B. L. Gordon, *Arch. Ophth.*, June, 1944, 31: 541.—(G. C. Leiner)

Arthrodesis in Tuberculosis of Hip.—In 45 cases of tuberculosis of the hip, 57 arthrodeses were done, 10 as secondary and 2 as tertiary procedures. In 60 per cent of the cases the diagnosis was proved by bacteriological and histological examination. An extraarticular arthrodesis without removal of the cartilage was performed in 53 cases and a combined extra- and intraarticular method only in 3 cases. Preoperative conservative care con-

sisting of bed-rest, high caloric diet, light exposure and orthopedic measures to the affected hip, at least in children, was usually followed by improvement of the general condition and by subsidence of local symptoms. The operation seems to be contraindicated in patients of less than 6 years of age since no patient operated on obtained a bony fusion. The operation is relatively contraindicated in children between 6 and 9 years of age because of an apparent slow healing of the bones and the soft tissues. The operation is contraindicated in the presence of a known abscess formation at the hip because of poor results as to the incidence of fusion and to the appearance and persistence of postoperative sinuses. Following the closure of the sinuses the prognosis of the operation is definitely better. The likelihood of fusion with complete operative program is good and fusion was obtained in 84 per cent of the adequately followed patients.—*Results following Arthrodesing Operations for Tuberculosis of the Hip, F. B. Roth, Bull. Hosp. Joint Dis., October, 1942, 3: 153.*—(F. G. Kautz)

Koch's Discoveries and Dermatology.—The great discoveries in bacteriology came at a time when dermatology was in its cytopathological phase after having passed through the purely morphological phase. Under the impact of bacteriology the etiologic concepts now are a synthesis of the former two phases. After a review of the forerunners of Koch and Pasteur, the author describes the immense achievements of Robert Koch and the benefit which dermatology drew from them. He deplores the indiscriminate employment of the word "allergy," the meaning of which is obscured. It is only the expression of a reactive and inflammatory effect and not the cause of a disease. The knowledge of tuberculosis etiology made it possible to establish clear clinical entities in dermatology. The reaction of the body to tuberculin is discussed. Nicolle believes that a lysine is present in the blood of the tuberculous patient which acts on the injected tuberculin and produces a toxic product which gives rise to local and general

reactions. The intracutaneous reaction to tuberculin was the starting point for similar tests in other diseases. Vitón believes that a benign bacteremia explains many symptoms of low grade reactions, especially in acne. Bacterial toxins are liable to disturb the functions of the vessels and the parenchyma and may even modify their anatomical structures. It has been almost forgotten that medicine owes to Robert Koch the first application of atoxyl in trypanosomiasis which was a forerunner of arsphenamine. Ehrlich himself acknowledged that the study of atoxyl opened the way for the discovery of arsphenamine.—*Influencia de los descubrimientos de Koch en dermatología, N. V. Greco, Rev. Asoc. méd. argent., December 15, 1943, 523: 1058.*—(W. Swienty)

Tubercle Bacillus and Endocrine Diseases.—An analogy is drawn between bacteriology and endocrinology. After the discoveries of Koch and Pasteur opened a new field of science, bacteriology, we see to-day a rapid succession of new discoveries in endocrinology. The results are often surprising. The pathology of the suprarenal glands is linked to the lesions produced by the tubercle bacillus. Of the first 11 cases published by Addison in his famous monograph, 5 had bilateral and one had one-sided tuberculosis of the adrenals. Tuberculosis of the adrenals causes a clinically well defined syndrome. Also of importance in endocrinology is tuberculosis of the ovaries and the adnexa. Tuberculous lesions in other endocrine glands play a rôle only in individual cases.—*El bacilo de Koch en las endocrinopatías, E. B. del Castillo, Rev. Asoc. méd. argent. December 15, 1943, 523: 1069.*—(W. Swienty)

Anatomy of Pleura and Endothoracic Fascia.—Microscopically there is a difference between the costal and the apical pleura. The pleura consists of (1) epithelial cells, (2) a thin underlying connective layer which has no vessels, (3) a thin superficial fibro-elastic layer, (4) a layer of connective tissue, containing few elastic fibres but rich in capillaries and arterioles.

This layer is about 0.25 mm. thick and contains sometimes numerous fat islands. This layer is often thickened and edematous and is followed by another thick structure, about 0.25 mm., which is firm and composed of fibro-elastic tissue: the endothoracic fascia. From the endothoracic fascia elastic fibres go to the aponeurosis of the intercostal muscles. Between the endothoracic fascia and the inner surface of the ribs there is a layer of extrafascial connective tissue, which is rich in fat and gradually loses itself into the intracostal structures. From the point of view of the microscopical structure, a separation can be obtained surgically within the fascia, in the subpleural connective layer and, extrafascially, in the extrafascial connective tissue. In the presence of inflammatory changes, however, all these layers disappear and are replaced by scar tissue. Above the first rib there is no endothoracic fascia. The latter loses itself gradually and the remains merge with the periosteum of the first rib. Here the thoraco-cervical diaphragm may be found, which consists of firm collagenous connective fibres and is almost entirely free of elastic fibres. Its insertion is at the upper border of the first rib. A separation of the lung in this region can be obtained only under the diaphragm. In conclusion, therefore, a separation of the pleura from the ribs can be best obtained below the first rib in the layer of the extrafascial connective tissue and above the rib under the thoraco-cervical diaphragm.—*Étude histologique sur les plèvres costale et apicale et sur le fascia endothoracique*, A. Policard & P. Galy, *Acta med.-chir. appar. respirat.*, 1942, 15: 1.—(G. Simmons)

Electrobiogenesis.—Blood is an electric complex in which energy originating in the outside world is accumulated and transformed. In the healthy individual the blood has a negative charge. In the sick organism the difference between the electric charge of the blood and that of the tissues is smaller than in the healthy individual. Health and disease are expressions of this changing dielectric state of the blood constituents. The basic principle

in all diseases is the difference in the electric potential and treatment should be directed toward improving the dielectric state of the organs and their ionization. Contrary to Tschejevsky, who thinks that the decrease in the electric charge in the sick individual is due to an insufficient amount of ions present in the environment (and who consequently tries to increase the ion concentration of the environmental air to obtain therapeutic results), Parodi tries to explain this phenomenon on the basis of an impaired absorption of ions and an increase in their dispersion, caused by changes in the electric-chemical structure of the blood. Whereas Tschejevsky assumes that the ions penetrate into the body through the lungs, Parodi feels that the electric field of the blood and skin is important.—*Elettrobiogenesi e stati patologici. Storia dell'evoluzione del piano delle nostre ricerche*, F. Parodi, *Lotta contro la tuberc.*, 1942, 13: 87.—(G. Simmons)

Blood-pressure and Respiration.—Following intravenous injection of acetylcholine and histamin in dogs an increase in the respiratory volume, associated with an increase in the alveolar oxygen and a decrease of the carbon dioxide tension, was noted. This action of acetylcholine is partly due to stimulation of the chemoreceptive organs located in the arch of the aorta and in the carotid sinus, while that of the histamin is simply due to a fall in blood-pressure.—*Blutdruck und Atmungsregulation*, H. Loeschke, K. Loose & W. Schoedel, *Pfluegers Arch.*, 1941, 245: 210.—(G. Simmons)

Oxygen Tension of Arterial Blood and Alveolar Air.—There is disagreement in the literature about the normal oxygen tension in human arterial blood. Studies were therefore done with a new method, which is described in detail. In 13 normal young adults at rest in semi-recumbent position an average arterial oxygen tension of 97.1 mm. Hg was found. Simultaneously collected alveolar air samples revealed an average oxygen pressure of 97.4 mm. Hg in end-expiratory samples. There was no difference between alveolar and arterial oxygen tension in healthy resting sub-

jects at sea level.—*The Oxygen Tension of Arterial Blood and Alveolar Air in Normal Human Subjects*, J. H. Comroe, Jr. & R. D. Dripps, Jr., *Am. J. Physiol.*, December, 1944, 142: 700.—(G. C. Leiner)

Circulatory Effects of Gasps, Yawns and Sighs.—In dogs gross and net pressures were recorded from the right and left ventricles. (The net pressure is the gross pressure minus the intrathoracic pressure.) Normal inspiration increases venous return to the right heart and produces contour changes characteristic of larger and more prolonged effective ejection without significantly changing the duration of systole. In dying gasps, deep breathing, yawns and sighs, which are generally considered as respiratory acts, the venous return is markedly increased. In the presence of cardiac arrest, dying gasps pump blood through the lungs and temporarily provide blood flow to the vital areas, the central nervous system and heart. Effective net pressure as great as 50 mm. Hg in the pulmonary artery, 50 mm. Hg in the coronary arteries and 40 mm. Hg in the central nervous system arteries was created by dying gasps in dogs where cardiac action had ceased.—*Influence of Dying Gasps, Yawns and Sighs on Blood Pressure and Blood Flow*, R. A. Woodbury & B. E. Abreu, *Am. J. Physiol.*, December, 1944, 142: 721.—(G. C. Leiner)

Intrathoracic Pressure and Circulation.—Cardiac output was measured by the direct Fick method and by a modification of Stewart's method in dogs breathing oxygen and air at a pressure of 8 and 16 cm. of water below atmospheric, 8 and 16 cm. of water above atmospheric, and at atmospheric pressure. The control cardiac output determinations made with the Fick method showed considerable variation, while the control de-

terminations with the modified Stewart method showed little variation. The cardiac output determinations with the modified Stewart method showed that when air under a positive pressure of 16 cm. of water was breathed the cardiac output was decreased. The average decrease was 33 per cent of the control. When air under a negative pressure of 16 cm. was breathed there was little change in the cardiac output. Peripheral venous and right auricular pressures were measured simultaneously in dogs breathing air from a chamber in which the pressure varied from 20 cm. of water pressure above to 20 cm. below atmospheric pressure. When air under a positive pressure of 16 cm. of water was breathed the pressure fall from peripheral vein to right auricle was decreased. The average decrease was 72 per cent of the pressure fall when air under atmospheric pressure was breathed in one group of experiments and 64 per cent in another. When air under a negative pressure of 16 cm. of water was breathed the pressure fall from peripheral vein to right auricle increased. The average increase was 191 per cent of the control pressure fall in one group of experiments and 244 per cent in another. Since the cardiac output of the dog changes very little when air under a negative pressure of 16 cm. of water is breathed it would appear that the maintenance of a high peripheral venous pressure, when right auricular pressure is greatly decreased, is due to the fact that the veins become partially collapsed just before entering the chest and increase the resistance to the flow of blood to the right auricle. (Author's Summary).—*The Effect of Positive and Negative Intrathoracic Pressure on Cardiac Output and Venous Pressure in the Dog*, J. P. Holt, *Am. J. Physiol.*, November 1, 1944, 142: 594.—(G. C. Leiner)

STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS

WILLIAM H. FELDMAN,¹ H. CORWIN HINSHAW² AND FRANK C. MANN¹

The use of penicillin in combating successfully certain infectious diseases provided ample reasons for the expectation that other antibiotic substances would be found that could be applied effectively to microbial pathogens. An important addition to the present relatively small group of antibiotics that are sufficiently devoid of toxic manifestations to permit *in vivo* application is streptomycin. This substance was announced in January, 1944 by Schatz, Bugie and Waksman (1). The fact that streptomycin is effective against tubercle bacilli *in vitro* (2) and *in vivo* (3) and has a relatively low toxicity potential makes this antibiotic of much interest to the student of tuberculosis.

THE SUBSTANCE

Streptomycin is a product of a fungus similar to the organism designated *Actinomyces griseus* by Krainsky (4) in 1914 (figure 1). The natural habitat of this organism is presumed to be the soil. The substance designated by Schatz, Bugie and Waksman as streptomycin was obtained by these workers from two different strains of actinomyces. One strain was isolated from soil from a heavily manured field and the other strain was obtained from the throat of a chicken. Schatz, Bugie and Waksman expressed doubt whether this organism is normally resident in the body of animals.

The streptomycin we have used was a powder varying in color from light cream to slightly brown. The material was highly hygroscopic and obviously readily soluble in water. According to Waksman, Bugie and Schatz (5), streptomycin is insoluble in ether and acetone and highly resistant to decomposition. A considerable decrease in activity occurs when the pH is reduced to 6 or less and a similar loss of activity has been noted in the presence of 2 per cent glucose. Solutions containing streptomycin can be heated to 60 C. (and above) for ten minutes without appreciable loss of activity, although a temperature of 120 C. for ten minutes is definitely deleterious (5).

When dissolved in water or in a physiological solution of sodium chloride and administered parenterally, streptomycin is readily absorbed and is likewise rapidly excreted. For this reason, unless administered continuously by the intravenous route, it is necessary to inject the material frequently if demonstrable concentrations in the blood are to be maintained (6).³

The first report on the effect *in vivo* of streptomycin against specific infections was that of Jones, Metzger, Schatz and Waksman (7). These workers found streptomycin to be effective in combating experimental infections in mice due

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³ Additional information regarding the biological properties of streptomycin and data pertaining to streptothricin and how this latter antibiotic differs from streptomycin will be found in the paper by Waksman, Bugie and Schatz (5).

to *Salmonella Schottmülleri*, *Pseudomonas aeruginosa* and *Shigella gallinarum*. In addition they found that streptomycin afforded protection against infection of chick embryos with *Shigella gallinarum* and with *Brucella abortus*. Robinson, Smith and Graessle (8) found streptomycin to have considerable activity *in vitro* against many aerobic gram-positive and gram-negative pathogens. However, certain gram-positive anaerobes, such as *Clostridium tetani*, *Clostridium Welchii*, *Clostridium septicum* and *Clostridium sordellii*, proved fairly resistant *in vitro* to streptomycin. *In vivo* studies by Robinson, Smith and Graessle confirmed the previously reported (7) observation that streptomycin was an effective agent in combating experimental infections due to *Salmonella Schottmülleri* and, in addition, that experimental infections caused by *Diplococcus*

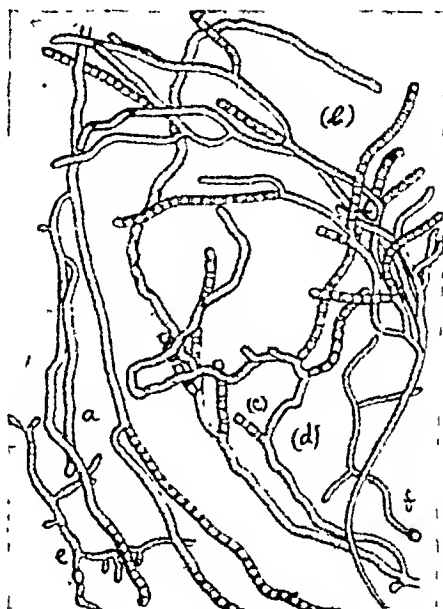


FIG. 1. *Actinomyces griseus*, with a short mycelium and abundant branching: a, b, c portions of aerial mycelium; d, e, spores germinating with one and two germ tubes respectively. (After Drechsler from Waksman's Principles of Soil Microbiology, Williams & Wilkins Co., Baltimore, 1932. Reproduced by permission of the author.)

pneumoniae and by *Staphylococcus aureus* could be readily controlled by adequate doses of the drug. Heilman (9) studied the *in vitro* and *in vivo* activity of streptomycin for *Pasteurella tularensis*. He found this microorganism to be one of the most sensitive to streptomycin of a number of gram-negative bacteria studied *in vitro*. In tests *in vivo* in which mice were infected with *Pasteurella tularensis*, streptomycin had a markedly protective effect. Heilman (10) also reported recently on the striking antibiotic effect of streptomycin *in vitro* and *in vivo* against microorganisms of the Friedländer group (*Klebsiella*).

Schatz and Waksman (2) studied the effects *in vitro* of streptomycin on a human strain of *Mycobacterium tuberculosis* (H37), with results indicative of bacteriostatic and bactericidal activity. They also noted that a strain of the avian variety of *Mycobacterium tuberculosis* was more resistant to streptomycin

than was true of the human strain studied. Schatz and Waksman, however, mentioned that a second antibiotic factor had been obtained from *Actinomyces griseus*. Unlike streptomycin, the second antibiotic substance is ether-soluble and was found to be more effective, *in vitro*, against the avian variety than against the human variety of *Mycobacterium tuberculosis*.

FIRST EXPERIMENT⁴

Our first supply of streptomycin was obtained from Dr. S. A. Waksman⁵ in April, 1944. The material had a potency of 37 units per milligram.⁶ The amount available was sufficient to provide treatment of 4 guinea pigs only.

Method: Twelve male guinea pigs weighing approximately 500 g. each were inoculated subcutaneously in the sternal region with 0.1 mg. of a sixteen day old culture of human tubercle bacilli, strain H37RV. The culture was grown in the modified synthetic liquid medium of Proskauer and Beck (11). Eight of the infected animals received no medicament; these served as controls both for this and for additional chemotherapeutic studies being done concurrently. Administration of streptomycin to 2 of the animals was started on the day of inoculation with *Mycobacterium tuberculosis*, while treatment of the other 2 animals was delayed for two weeks.

The dose of streptomycin for the guinea pig was set arbitrarily at 75 mg. (2,775 units) for each twenty-four hour period. One of the 2 animals in which treatment was started immediately after infection received only half of this amount. The substance was given subcutaneously five times daily at three-hour intervals. The first injection of each day was at 9:00 a.m. and the last injection at 9:00 p.m.⁷

Since a daily dose of 75 mg. (2,775 units) of streptomycin was tolerated satisfactorily by the one animal in which treatment with this amount was started at the time of inoculation with *Mycobacterium tuberculosis*, a similar dose was used to treat each of the 2 remaining animals, starting on the fifteenth day after infection.

Treatment was continued until the fifty-fourth day of infection, when the supply of streptomycin was exhausted. At the termination of treatment the 4 animals receiving streptomycin were killed for necropsy. During the preceding two weeks, 2 of the untreated controls had died. To provide additional material for comparison 2 more controls were killed. The remaining 4 animals in the control group were killed sixty days after infection.

At the time of necropsy the spleen of each of the 4 animals that had received streptomycin was removed aseptically. The spleens were divided approximately

⁴ A preliminary report of our first and second experiments with streptomycin in tuberculous guinea pigs has been published previously (3).

⁵ New Jersey Agricultural Experiment Station, New Brunswick, New Jersey.

⁶ In this instance a unit of streptomycin as defined by Jones, Metzger, Schatz and Waksman (7) consisted of that quantity of the antibiotic agent necessary to inhibit the growth of a certain strain of *Escherichia coli* in 1 cc. of nutrient broth or agar.

⁷ We express our gratitude to our colleague Dr. F. R. Heilman for important and valuable assistance in the first experiment.

into two equal portions; one portion was preserved for subsequent histological study and the other was ground and suspended in sterile physiological solution of sodium chloride. Each splenic suspension was used to make cultures and to inoculate subcutaneously 2 normal guinea pigs. The recipients were killed for necropsy fifty-six days after inoculation.

✓ *Toxicity:* In the dosage used, streptomycin appeared to be well tolerated by each of the 4 animals, since all apparently remained in good health. Each of the 4 guinea pigs increased in weight. However, the greatest gain occurred in the 2 animals that had received streptomycin for the shorter period.

The hemoglobin values of the treated animals, determined from blood specimens removed by cardiac puncture at the time of necropsy, were but slightly below normal and in no sense critical. The values expressed in grams per 100 cc. of blood were 12.8, 12.8, 13.2 and 12, respectively. The average value for the 4 treated animals was 12.7 g., a figure that was in excess of the average hemoglobin value of the 6 untreated controls killed for necropsy, which was 11.

A further indication of the lack of toxicity of streptomycin in the doses given was the absence of recognizable tissue changes in the kidneys, adrenals, liver, lungs, urinary bladder, lymph nodes and bone marrow of each of the treated guinea pigs. Unlike most of the sulfone compounds which we have studied, streptomycin did not induce large, dark spleens (12).

✓ *Antituberculosis effects:* The rather severe and widely distributed tuberculosis that occurred in the guinea pigs constituting the untreated control group provided satisfactory material for judging the effect which was exerted by streptomycin. The disease was strikingly evident grossly in each of the controls and microscopically the lethal destructiveness of the advancing tuberculous process was characteristic and at marked variance with the situation in the animals treated with streptomycin (figure 2). The amount of tuberculosis in the subcutis at the site of injection and in the contiguous lymph nodes was minimal in 3 of the 4 animals treated with streptomycin. In one guinea pig, lesions were not found in either of these situations. Among the treated animals the amount of visceral tuberculosis was likewise minimal. Among the 4 spleens there was only one in which tuberculosis was recognizable grossly and in this instance the involvement consisted of a single nodule 0.1 cm. in diameter.

On microscopic examination a few lesions were found which could not be seen grossly but the changes in the spleens were quantitatively of minor degree and when present were definitely nonprogressive or even retrogressive (figure 3). The same was true of the lungs and livers of the animals treated with streptomycin. The disease either was not present or when found was minimal and arrested or nonprogressive. Based on the arbitrary selection of the numeral 100 as representing the theoretical maximal amount of tuberculosis possible, the average numerical index of infection for the 4 guinea pigs treated with streptomycin was 2.8. For the 8 controls the average index of infection was 81.9⁸

✓ *Mycobacterium tuberculosis* was recovered in cultures made from the spleens

⁸ The procedure for recording the character and extent of experimental tuberculosis has been described in another paper (13).

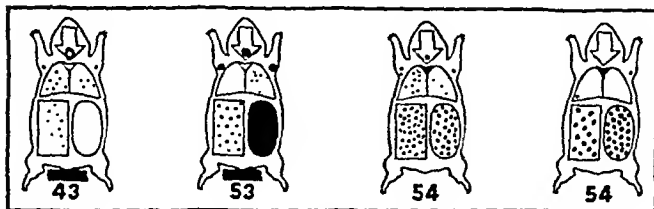
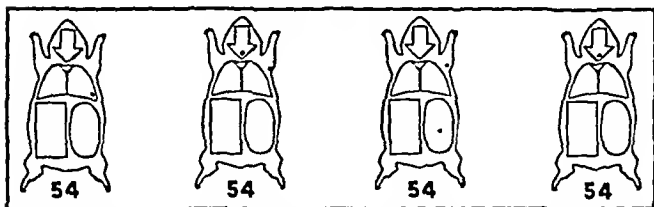
CONTROLS**TREATED**

FIG. 2. Amount of tuberculosis noted grossly in treated and untreated animals, shown schematically. The numerals indicate the length of life in days after infection. The black bar indicates that the animal died (first experiment). For further explanation of symbols used see figure 1 of reference 11.



FIG. 3a. Advancing, destructive tuberculosis, liver of untreated control. Killed fifty-four days after inoculation ($\times 104$) (first experiment). b. Small epithelioid tubercle, spleen of guinea pig treated with streptomycin beginning two weeks after infection ($\times 104$). No lesions found in lungs or liver (first experiment).

of only one of the guinea pigs treated with streptomycin. The animal had received a daily dose of 1,387 units of streptomycin for fifty-four days—the entire period of the infection. Although the failure of a larger number of cultures to

be obtained from the splenic suspension was suggestive of marked bactericidal effects, the tentative impression was eventually dispelled by the results of the animal inoculation tests. These results showed that viable and virulent tubercle bacilli were actually present in each of the spleens of the 4 treated animals. This was demonstrated by the fact that tuberculosis was present at necropsy in one or both of the 2 normal recipients that had been inoculated with the splenic suspensions from each.

The results of the first study, while based on inadequate data, were sufficiently impressive to justify additional *in vivo* studies with streptomycin.

SECOND EXPERIMENT

Methods: Each of 20 male guinea pigs, each weighing approximately 500 g., was inoculated subcutaneously in the sternal region with 0.1 mg. of a culture of *Mycobacterium tuberculosis*. Ten were inoculated with strain H37RV and 10 with a strain (3728) isolated within the past year from the sputum of a patient suffering from pulmonary tuberculosis.⁹ The animals were divided into two equal groups, each group containing 5 animals inoculated with strain H37RV and 5 inoculated with strain 3728. One group of 10 animals was to be treated with streptomycin and the other 10 were to serve as controls.

Streptomycin was administered to 6 animals—3 inoculated with H37RV and 3 with strain 3728—beginning the same day as the infective inoculum was introduced. Treatment of the other 4 animals—2 inoculated with H37RV and 2 with strain 3728—was delayed until the fifteenth day after inoculation. Treatment was continued until sixty-one days after the animals had been infected. The treated animals and the untreated controls were then killed for necropsy. At the time of necropsy blood was taken by cardiac puncture for the determination of hemoglobin values and a study of the morphological aspects of the blood. Approximately half of each spleen was removed aseptically and, after appropriate preparation, was cultured for *Mycobacterium tuberculosis*. Tissues from the spleen, liver, lungs and kidneys, the site of inoculation and the axillary space, including the axillary lymph nodes, of each animal were preserved for subsequent microscopic examination.

Dosage of streptomycin: The streptomycin available when the second experiment was started was supplied by Doctor Waksman and represented a different lot of the substance from that furnished by him for the first experiment. Each of the 6 guinea pigs in which treatment was started on the day of infection received a daily dose of streptomycin of 3,500 units divided into four daily doses at six-hour intervals. In all instances the streptomycin was dissolved in sterile physiological solution of sodium chloride and injected subcutaneously. At the end of one week of treatment the weight of each of the animals either had remained stationary (one guinea pig) or had decreased (5 guinea pigs); consequently the daily dose of streptomycin was temporarily reduced to 1,750 units. This dose schedule was continued for the ensuing nineteen days, when a more purified lot of streptomycin was received from Doctor Waksman. The dose was

⁹ Previous observations had revealed this latter strain to be fully virulent for guinea pigs.

then increased to 3,000 units daily for a period of fifteen days. A further refined product was then received and the dose was increased to 6,000 units.¹⁰ This dose was maintained for the next twenty days, at the end of which the experiment was terminated. The dose schedule for streptomycin for the 4 animals in which treatment was delayed until the fifteenth day of infection was the same as that being currently employed for the other animals.

Toxicity: The preparation of streptomycin used in the earlier phase of the second experiment was tolerated less satisfactorily than was true of the streptomycin used in the first experiment. As mentioned previously, most of the animals lost weight after administration of the substance had been started. In one case edema and congestion of the external genitalia developed and the animal finally died after having received streptomycin for only nine days. At necropsy the important lesions were those of severe acute peritonitis. Structural changes indicative of hepatic damage were not seen microscopically. One other animal experienced considerable loss of weight, which continued even after the daily dose had been reduced to 1,750 units. Treatment was withheld intermittently in order to permit the animal to recover its loss of weight. After the more refined product was obtained, no further difficulty was experienced. At the end of the experimental period each of the 9 surviving guinea pigs weighed more than at the beginning. The gain in body weights varied from 85 g. to 300 g. with an average gain of 177 g. for the 9 animals.

The concentrations of hemoglobin for the 9 surviving animals that were treated with streptomycin varied from 11.6 to 13.6 g. per 100 cc. of blood, the average being 12.8 g. The hemoglobin values for 8 of the 9¹¹ untreated controls that survived the sixty-one day period of observation varied from 5 to 13.6 g., the average being 11 g. Studies of the morphological aspects of the blood picture revealed nothing of significance.

Except in 2 instances in which a few small subcapsular hemorrhagic infarction-like changes were seen in the liver, microscopic examination of the tissue of the animals that had received streptomycin failed to disclose in the parenchymal organs recognizable changes that could be interpreted as evidence of toxic effects. In some instances the tissue from the axillary space, which was the site of frequent injections of streptomycin, showed some cellular reaction, edema and hemorrhage of minor degree.

✓ *Antituberculosis effects:* As was true in the first experiment, there was a marked and striking difference in the results of the tuberculous infection between the controls and the treated animals. This was evident from the gross appearance of the respective animals at necropsy (figure 4). The disease in the untreated controls was widely disseminated and in most instances destructive. Among the animals that had received streptomycin the reverse was true, evidence of

¹⁰ Streptomycin for the completion of the second experiment and for the conduct of the third experiment was kindly supplied by Merck and Company, Inc., Rahway, New Jersey, through the courtesy of Dr. D. F. Robertson, Dr. R. T. Major, Dr. Hans Molitor and Dr. J. M. Carlisle.

¹¹ The hemoglobin value of one of the controls was inadvertently not determined.

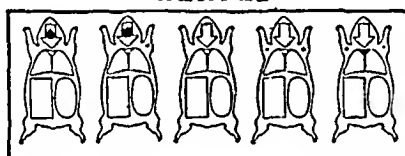
the disease being absent or barely detectable. The disease had in most instances remained localized at the site of inoculation and the contiguous lymph nodes of the axillary region. In only one of the treated animals was tuberculosis observed grossly in any of the organs. In this instance the spleen contained two minute foci. In 2 of the 9 treated guinea pigs tuberculous involvement of the tracheobronchial lymph nodes was noted by careful palpation of these structures. The differences in the amounts of tuberculosis in the treated and untreated groups of guinea pigs are given in table 1.

Streptomycin—2nd exper. Infected 61 days

CONTROLS - NOT TREATED



TREATED



TREATMENT DELAYED

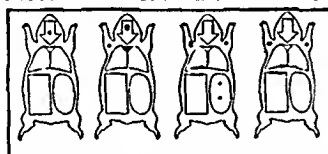


FIG. 4. Schematic representation of the amount of tuberculosis recorded at the time of necropsy in treated and untreated groups of guinea pigs. Treatment of the animals represented in the middle group was started the day the animals were inoculated with *Mycobacterium tuberculosis*. In the lower group treatment was delayed for two weeks (second experiment).

Microscopically, the disease in the 9 untreated controls revealed the usual advancing morbid processes in the spleen, lungs and liver that one expects in guinea pigs after inoculation with virulent *Mycobacterium tuberculosis*. Microscopic examination of the spleen, liver and lungs of each of the 9 treated animals showed the situation to be entirely different. No lesions were found in the lungs of any of the guinea pigs, while the livers of only 2 were involved. These lesions were too small to be seen grossly, being exceedingly few and atrophic. No lesions were found microscopically in the spleens of 4 of the treated animals. In one, the tuberculosis was limited to a single microscopic focus composed largely of so-called foam cells, and in each of the other 4 an occasional solitary hard tubercle could be seen, which had not been noted grossly (figure 5). Inci-

dentally, the latter spleens were from the 4 animals in which treatment had been delayed for fifteen days after the animals had been infected.

TABLE 1
Summary of results obtained in experiment 2

GROUP	ANI- MALS	DURATION OF INFECTION		DURATION OF TREAT- MENT	ORGANS SHOWING MACRO- SCOPIC TUBERCULOSIS			INDEX OF INFECTION DETER- MINED MICRO- SCOPICALLY*
		Died	Killed		Spleen	Liver	Lungs	
		<i>days</i>	<i>days</i>	<i>days</i>				
Controls (9 animals†)	9	0	61	0	8	7	7	67
Treated (9 animals†)	4	0	61	47	1	0	0	5.8
	5	0	61	61	0	0	0	

* Tissues examined included spleen, liver, lungs, tracheobronchial lymph nodes, subcutis at the site of injection and the axillary lymph nodes (100 units represents theoretical maximal amount of tuberculosis possible).

† Of the 10 animals in the group originally, one died prematurely.

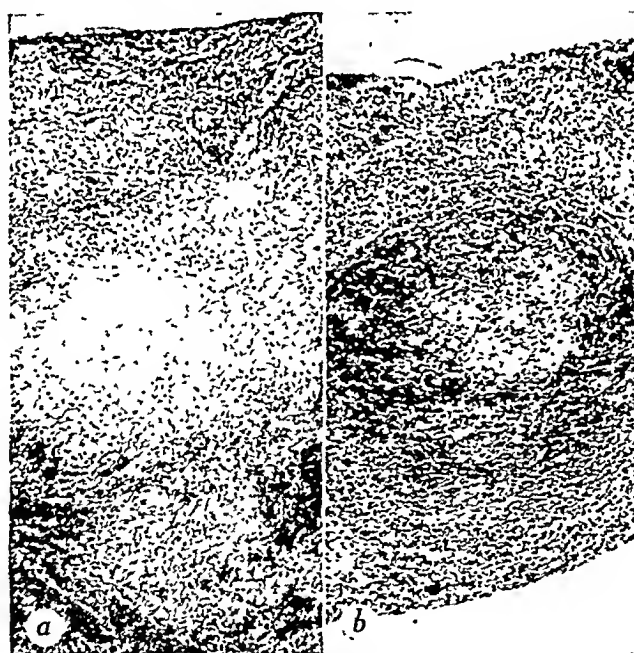


FIG. 5a. Severe tuberculous changes in spleen of untreated control ($\times 50$) (second experiment). b. Atrophic remnants of the only tuberculous lesion found in the spleen of guinea pig treated with streptomycin beginning two weeks after inoculation ($\times 115$) (second experiment). The 2 animals represented in figure 5 were both killed sixty-one days after inoculation with *Mycobacterium tuberculosis*.

Expressed numerically (13), the index of infection for the untreated controls was 67; for the animals that had received streptomycin the figure was 5.8. There was no recognizable difference in the ability of the streptomycin to affect favorably infection induced by strain H37RV and strain 3728.

The attempts to recover *Mycobacterium tuberculosis* by culture from the splenic tissue of treated guinea pigs resulted in positive results from the spleens of 3 animals and negative results in 6. Two of the 3 positive results were obtained from the spleens of animals in which the beginning of treatment had been delayed. Each of the animals in which *Mycobacterium tuberculosis* was recovered had been inoculated with strain H37RV.

Sensitivity to tuberculin was demonstrated in 7 of the treated animals at the termination of the experiment. In 2 guinea pigs the results of the tuberculin test were indefinite.

The results of the first two experiments with streptomycin revealed this substance as one capable of considerable antibiotic influence against infections induced in guinea pigs with the human variety of *Mycobacterium tuberculosis*. Not only did the antibiotic prevent, in a large measure, the development of tuberculosis in guinea pigs when treatment was started on the same day that the animals were inoculated, but, in addition, impressive deterrent suppressive effects were accomplished in those animals that had been inoculated two weeks prior to the beginning of treatment. The relatively low toxicity of streptomycin *in vivo* and the desirability of determining the true measure of its therapeutic effectiveness in experimental tuberculosis of guinea pigs prompted a desire to continue and expand our studies. As a consequence a third experiment was done.

THIRD EXPERIMENT

The objective of the third study was primarily to impose conditions sufficiently severe so as to obtain, if possible, unequivocal evidence as to the ability of streptomycin to exert a therapeutic effect against experimental tuberculous infections. In order to be sure of creating in at least some of the experimentally infected animals a well established disease entity before treatment was started, the animals were inoculated several weeks before the administration of streptomycin was begun. As a source of additional evidence of whether or not streptomycin was capable of exerting a definite therapeutic effect on experimental tuberculous infections, we proposed to obtain by biopsy tissues from the infected animals before treatment was started and to compare eventually the tissue obtained at biopsy with that obtained from the same animal at necropsy after the period of treatment had terminated.

Methods: Sixty male guinea pigs whose average weight was slightly in excess of 0.5 kg. were obtained. Fifty of the animals were inoculated subcutaneously in the sternal region with 0.001 mg. of a nine day old culture of *Mycobacterium tuberculosis*, strain H37RV. The 10 remaining guinea pigs received in a similar manner 0.001 mg. of a thirty-eight day old culture of our strain 3728.¹² The animals were caged in pairs. The animals were tested with tuberculin (intracutaneous injection of 0.02 to 0.04 cc. of Old Tuberculin 1:100) forty-two days

¹² As mentioned previously, this strain of *Mycobacterium tuberculosis* had been isolated during the past year from a patient who had pulmonary tuberculosis and was used to inoculate some of the animals in the second experiment.

after being inoculated with *Mycobacterium tuberculosis* and all gave a positive reaction. On the forty-eighth day after infection all animals were anesthetized with pentobarbital sodium and laparotomy was performed by one of us (F. C. M.) for the purpose of obtaining a specimen for biopsy from the liver of the respective animals. The day following the laparotomies the surviving animals were divided into two groups of approximately equal size.¹³ One group was to

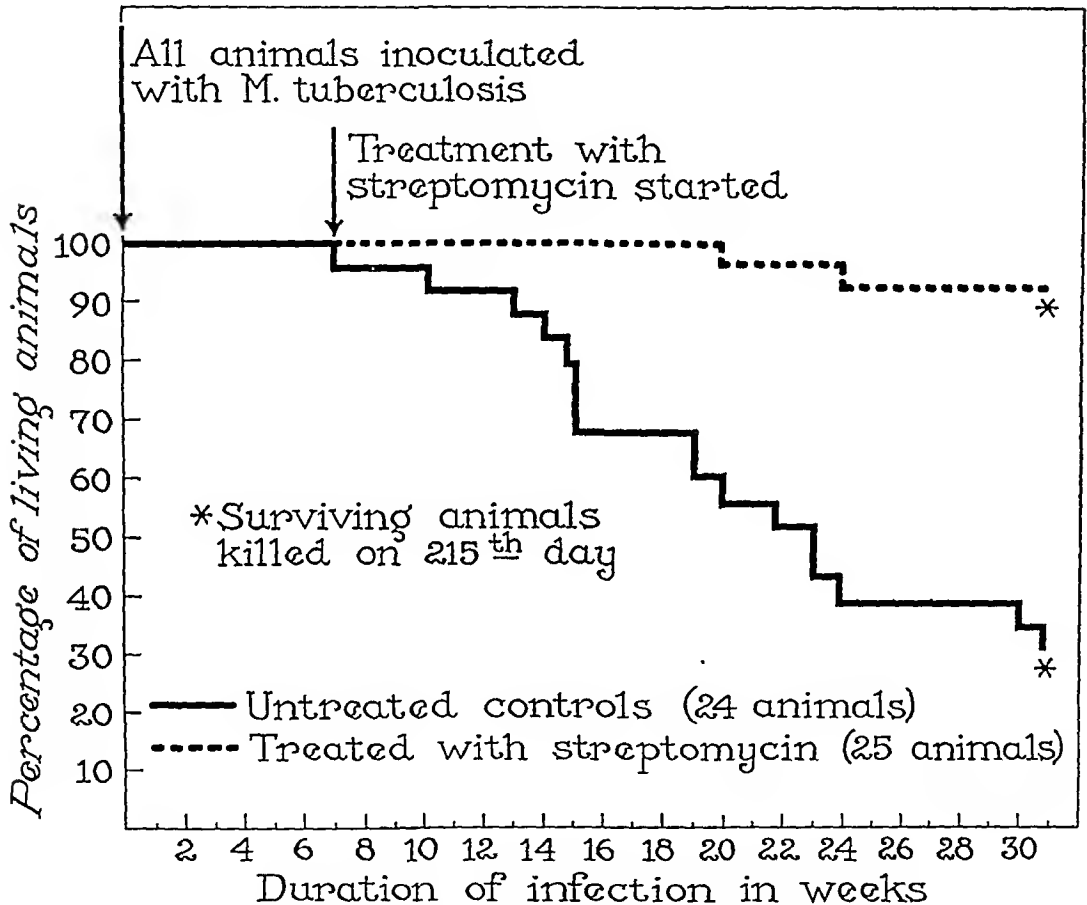


FIG. 6. Comparative survival times of treated and untreated groups of guinea pigs (third experiment).

serve as the untreated controls and the other group was to receive treatment with streptomycin. As a consequence of the deaths of 3 guinea pigs during the eight days following laparotomy, the animals finally constituting the group that was to receive treatment totaled 25. In the group that did not receive treatment the number of animals totaled 24.

¹³ Of the 60 guinea pigs that were subjected to laparotomy, 7 failed to recover from the anesthetic and 3 died during the eight days following laparotomy. Indicative of the progressive character of the tuberculous infection was the fact that visceral tuberculosis was recognizable in 8 of the 10 guinea pigs that died immediately or soon after laparotomy was performed.

Throughout the period of medication each animal in the treated group received subcutaneously at six-hour intervals 1,500 units of streptomycin or a total of 6,000 units of the drug every twenty-four hours. The medication was started on the forty-ninth day after inoculation and continued without interruption for 166 days, when the experiment was terminated. The animals had been inoculated 215 days previously. Before the experiment was terminated, all guinea pigs in the treated and in the untreated groups of guinea pigs were again tested for sensitivity to tuberculin.¹⁴ One-half of the spleen of each guinea pig treated with streptomycin was obtained aseptically at the time of necropsy and subsequently examined for the presence of tubercle bacilli. The respective spleens were ground and suspended in physiological solution of sodium chloride. Each suspension was then used to "seed" 8 slants of Sasano-Medlar (14) medium and to inoculate 2 normal guinea pigs subcutaneously. The results of the cultural attempts were recorded after ten weeks of incubation. The guinea pigs inoculated with the splenic suspensions were killed for necropsy after being kept under observation for eight weeks.

Comparative survival times: During the 215 days of the experiment there was a marked dissimilarity in the mortality of the two groups of animals. In the group that was not treated approximately 70 per cent died, while, among the 25 animals that were receiving streptomycin, only 2 (8 per cent) had died (figure 6). Sixteen (approximately 94 per cent) of the deaths among the untreated group occurred during the first 169 days after inoculation with *Mycobacterium tuberculosis*. During the same period the only 2 deaths that occurred among the treated animals were recorded. As may be noted, the 2 treated animals died 146 days and 168 days, respectively, after infection.

Antituberculosis effects: Impressive differences existed in the amounts of tuberculosis seen in the two groups of guinea pigs. The differences were strikingly apparent when the results of the necropsies of the respective animals were recorded schematically and arranged for direct comparison (figure 7). With the exception of the animal that died after 146 days of infection (ninety-eight days of treatment) and in which tuberculous splenic nodules were visible grossly, massive, wide-spread parenchymal tuberculous infection such as characterized the disease in most of the untreated controls (figure 8) did not occur.¹⁵ Not only was the therapeutic or deterrent effect of streptomycin apparent in the relative absence of gross parenchymatous lesions of tuberculosis in the organs of predilection, such as the spleen, liver and lungs, but of great interest were the relatively few instances in which tuberculous lymphadenopathy occurred. As recorded in figure 7, there were 8 animals which at the time of necropsy appeared to have tuberculous involvement of the tracheobronchial lymph nodes. Subsequent microscopic examination of these tissues failed to reveal tuberculous changes in 4.

¹⁴ As mentioned previously a 1:100 dilution of Old Tuberculin was used and the material was injected intracutaneously in 0.02 to 0.04 cc. amounts.

¹⁵ One of the treated animals had at necropsy severe bilateral tuberculous orchitis although no demonstrable disease was found in the liver or lungs and the disease in the spleen was limited to a few calcified nodules demonstrable microscopically.

The most impressive evidence of the therapeutic efficacy of streptomycin was the information obtained by comparing microscopically the tuberculous changes present in the biopsy specimens of the liver obtained before treatment

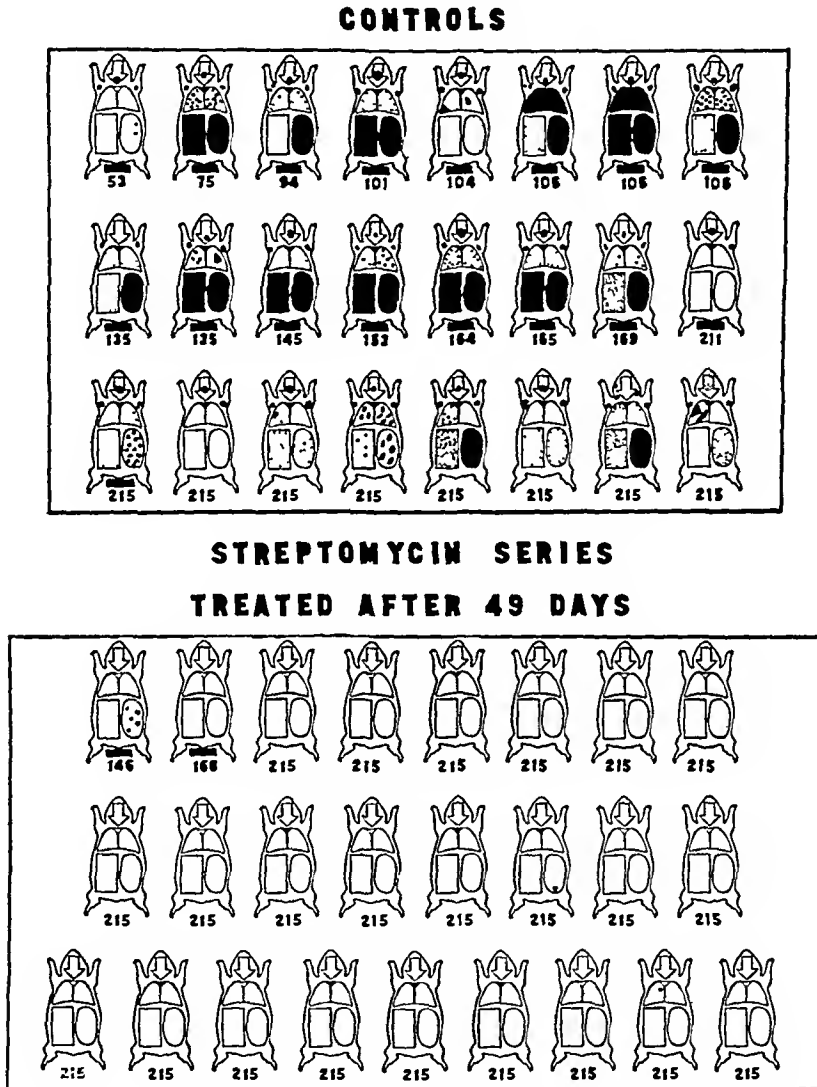


FIG. 7. Amount of tuberculosis, shown schematically, noted grossly at necropsy in treated and untreated groups of guinea pigs. The number beneath an animal represents the length of life in days after inoculation. A black bar above a numeral indicates that the animal died (third experiment).

was started with sections taken from the same livers after the period of treatment was terminated. As may be noted in figure 9, in those animals that did not receive treatment, the tuberculosis, which was well established when biopsy was done on the forty-eighth day after infection, continued to exhibit a destructive progressiveness that was in conformity with the expected unaltered course of inoculation tuberculosis in guinea pigs. The character of the tuberculous

changes in the biopsy specimens from the livers of the animals that were subsequently treated with streptomycin was comparable in every way to the situation present in the biopsies of livers of the animals that did not receive treatment subsequently. However, when the biopsy specimens from the animals that were treated were compared with material obtained at necropsy from the same livers at the end of the period of treatment there was demonstrable proof that the course of the disease had been definitely altered (figure 10). Instead of a



FIG. 8. Severe tuberculosis in the lungs, liver and spleen of untreated guinea pig that died 104 days after subcutaneous inoculation with 0.001 mg., strain H37RV.

continuing destructive process that was clearly apparent in the biopsy specimens when treatment started, a favorable influence had been exerted and after a prolonged period of treatment the hepatic lesions resolved or remained as atrophic remnants. Thus we have an example of a well established, potentially lethal, tuberculous disease in a highly susceptible animal becoming reversed under the influence of a medicament administered with therapeutic intent.

The histological examination of the tissues provided a considerable amount of information regarding the efficacy of the therapeutic procedure. Among the 25 animals treated—including one that died 146 days after infection and one

that died 168 days after infection—there were 13 devoid of gross or microscopic tuberculosis after 166 days of therapy. In only one animal was a tuberculous lesion found in the liver (figure 10) and in only one was a parenchymal lesion found in the lung. In the latter instance tuberculosis was represented by a solitary calcified nodule (figure 11). Fourteen of the 25 spleens were without tuberculous changes and none of the spleens had lesions of progressive or extensive disease. As a matter of fact, of the 11 spleens in which tuberculous lesions were found, in 7 the lesions were calcified, in 3 they were fibrotic and in one they consisted of epithelioid or hard tubercles (figure 12). Another impressive evidence of the therapeutic efficacy was the paucity of tuberculosis in



FIG. 9a. Tuberculosis in liver at time of biopsy in untreated control ($\times 130$). *b*. Destructive necrotizing disease in the liver at the time of death, 101 days after infection ($\times 130$). Same animal represented in *a* (third experiment).

the suprasternal tissues and in the contiguous lymph nodes. Since the animals had been inoculated in tissues overlying the sternum, one would expect to find residual lesions at the site of injection or in the lymph nodes draining this region. However, in only 2 of the 25 animals treated with streptomycin were tuberculous lesions noted. In both instances the disease was limited to a single axillary lymph node with no signs of infection in the suprasternal tissues.

The differences in the amounts of tuberculosis present at necropsy in the treated and untreated groups of guinea pigs have been summarized numerically and are shown in table 2. When reduced to a numerical basis the differences in the amount of tuberculous disease in the two groups of guinea pigs are of sufficient magnitude to constitute a real rather than an apparent difference.

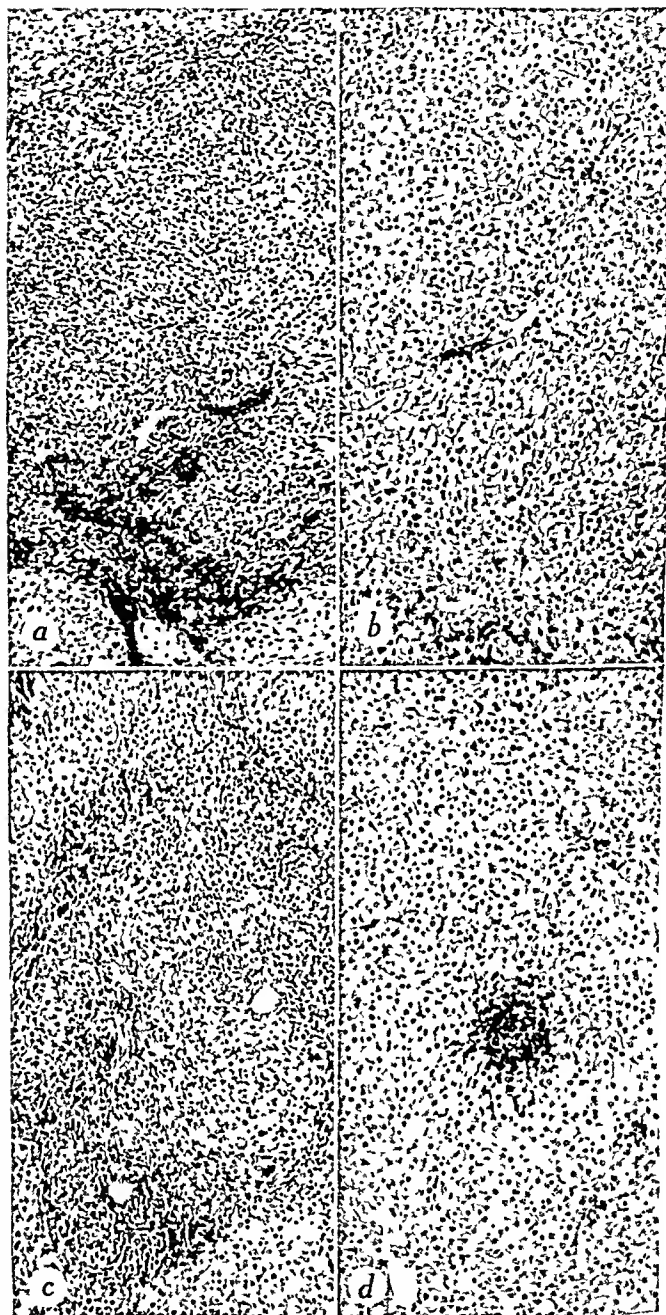


FIG. 10. Livers of guinea pigs before and after treatment with streptomycin (third experiment). *a.* Large tuberculous nodule at time of biopsy ($\times 130$). *b.* Same liver as shown in *a* after treatment for 166 days with streptomycin. Organ was free of demonstrable lesions ($\times 130$). *c.* Progressive tuberculous nodule in the liver, biopsy specimen ($\times 130$). *d.* Appearance of liver of same animal represented in *c* after 166 days of treatment with streptomycin. Disease limited to single atrophic focus ($\times 130$).

Residual infection in treated animals: It was determined by cultures and by animal inoculation tests that the streptomycin did not, under the conditions imposed, eliminate all tubercle bacilli from the spleens of all guinea pigs that

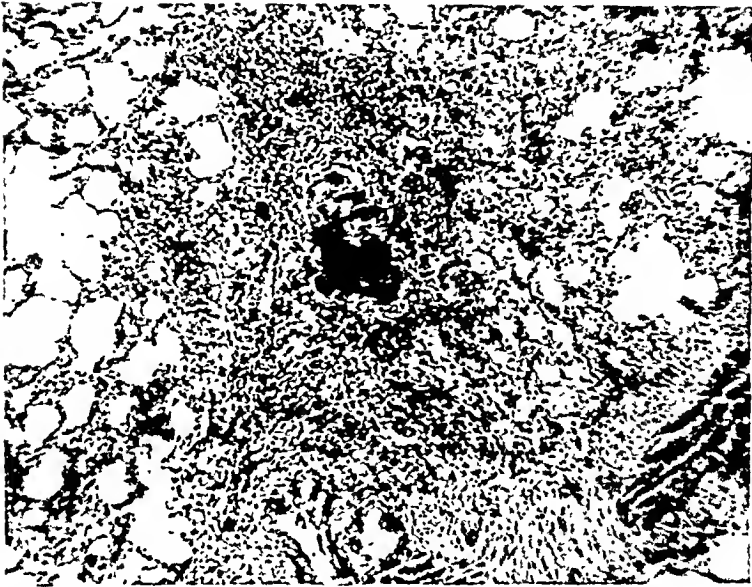


FIG. 11. Calcified nodule in lung of guinea pig treated with streptomycin for 166 days ($\times 130$). The only other lesion found was a small fibrotic nodule in the spleen (third experiment).

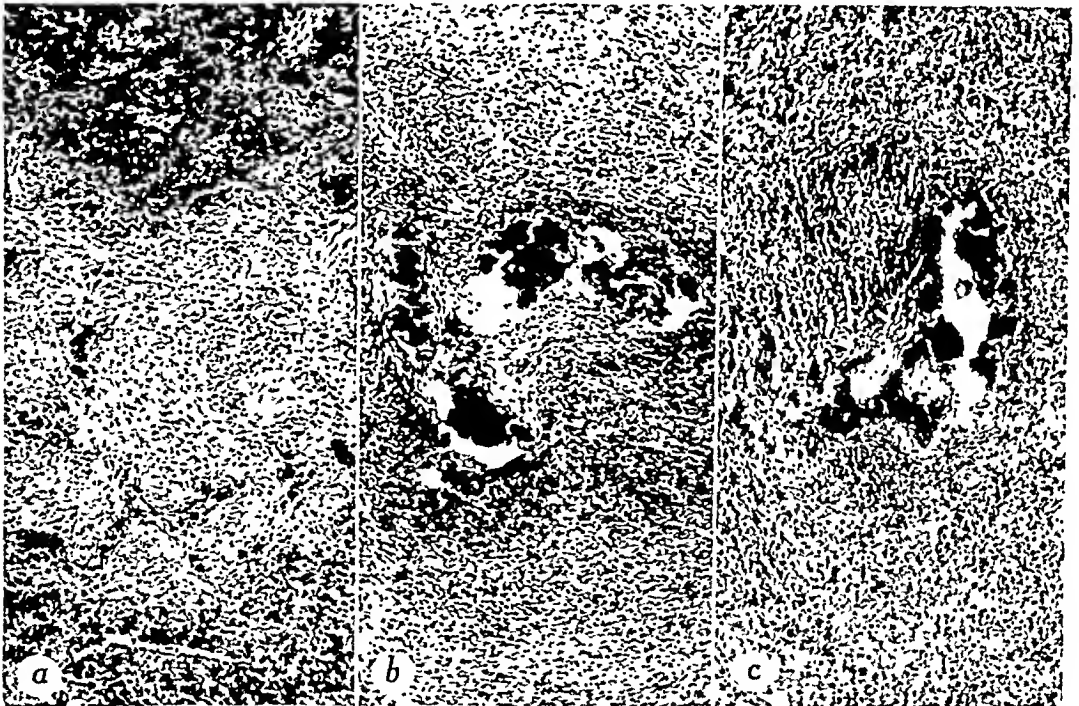


FIG. 12. Nonprogressive tuberculous lesions in spleen of 3 animals in the group treated with streptomycin (third experiment). *a*. Area of diffuse fibrosis in the spleen ($\times 130$). Animal had received streptomycin for 119 days. No lesions in lungs or liver. *b*. Contracted, retrogressive lesion with calcification ($\times 130$). Animal had been treated with streptomycin for 166 days. No other signs of tuberculosis found in any of the tissues. *c*. Solitary calcified nodule in the spleen of guinea pig treated with streptomycin for 166 days ($\times 130$).

had received treatment. By cultural procedures positive results were obtained from 8 of the 24 spleens.¹⁶ In 16 instances attempts to culture *Mycobacterium tuberculosis* were futile. The results of the animal inoculation tests were markedly different from those obtained by culture. Of the 23 spleens used for animal inoculation tests, 15 contained *Mycobacterium tuberculosis* capable of producing a mild to a severe tuberculous disease in the usual organs of predilection in at least one of the pair of animals receiving the respective splenic suspensions.¹⁷

It should be recalled that one-half of each spleen was preserved for the making of histological preparations and that the other half was prepared for tests to determine the presence of viable and virulent *Mycobacterium tuberculosis*. Since a portion of each spleen was available for microscopic study, it was possible to compare the morphological aspects of the respective spleens with the results of the tests for residual infection and to determine if the results of the latter tests could be correlated with the specific character of structural changes pres-

TABLE 2

Average severity of tuberculosis in different anatomical situations expressed numerically. Data based on the histopathological characteristics of the tissues indicated (13). (Experiment 3)

GROUP	ANIMALS	SPLEEN (MAX. 35)	LUNGS (MAX. 30*)	LIVER (MAX. 25)	SITE OF IN- OCULATION (MAX. 10†)	AVERAGE INDEX OF INFECTION (MAX. 100)
Controls.....	24	28	24.1	18.3	10	80.4
Treated.....	25	0.52	0.6	0.04	0.08	1.24

* Includes involvement of tracheobronchial lymph nodes when no lesions were found in the lungs.

† Includes contiguous lymph nodes.

ent in the spleens of the animals treated with streptomycin. The results show that, among the 15 spleens from the treated animals that were found to contain *Mycobacterium tuberculosis* at the end of the period of treatment, in 6 that portion of the respective spleens to be sectioned for histological study showed only calcified nodules. In 2 instances in which the animal inoculation test gave positive results, those portions of the respective spleens studied microscopically showed fibrotic foci. In 7 other instances in which the animal inoculation tests gave positive results, portions of the respective spleens studied microscopically failed to reveal tuberculous changes.

This phase of study indicated the unreliability of predictions as to the presence or absence in guinea pigs of virulent *Mycobacterium tuberculosis* based on

¹⁶ Results were considered positive when acid-fast bacillary forms having the colonial features of *Mycobacterium tuberculosis* grew on the surface of medium seeded with splenic material.

¹⁷ In 2 instances, tuberculosis in the animals previously inoculated with splenic material from treated animals was limited to minimal tuberculous lymphadenopathy of the axillary nodes in one of the 2 animals inoculated.

the structural character of the tuberculous lesions or whether tissues without demonstrable lesions of tuberculosis still harbor the causative organisms. Some of our results suggest the latter to be true, although it is obvious that the splenic tissues prepared for animal inoculation were not examined microscopically and conversely that the exact tissues examined microscopically were not used also to inoculate animals.

Sensitivity to tuberculin: As was mentioned previously, at the end of the experiment all surviving animals in the treated and untreated groups were tested for sensitivity to tuberculin one week before they were killed. Each of the untreated controls gave a markedly positive reaction, many showing the beginning of ulceration forty-eight hours after the tuberculin was introduced. With one exception the reaction to tuberculin among the treated animals was mild. Of

TABLE 3

*Results of tests to demonstrate residual infectivity in spleens of 9 guinea pigs treated with streptomycin and subsequently found to be negative to tuberculin**

ANIMAL	HISTOPATHOLOGICAL CHARACTERISTICS OF SPLEEN†	SPLENIC SUSPENSION	
		Culture	Pathogenicity for normal guinea pigs
1	Calcified nodule‡	+	Negative
2	No lesions	—	Negative
3	No lesions	—	Negative
4	No lesions	—	Negative
5	No lesions	—	Positive
6	No lesions	—	Negative
7	No lesions	—	Negative
8	Calcified nodule‡	—	Positive
9	No lesions	—	Negative

* All animals were sensitive to tuberculin prior to beginning of treatment.

† One-half of each spleen was used to prepare material for histopathological examination and the remainder for making cultures and the inoculation of guinea pigs.

‡ The demonstrable signs of tuberculosis were limited to the spleen.

the 23 animals that had been treated with streptomycin the reaction in 14 was recorded as positive, while in 9 the reaction to tuberculin was recorded as negative. The results of tests to determine the presence of viable or virulent *Mycobacterium tuberculosis* in the respective spleens of each of the 9 guinea pigs that failed to react to tuberculin are shown in table 3. The fact that the spleens of only 2 of the 9 animals that failed to react to tuberculin contained virulent *Mycobacterium tuberculosis* is of considerable interest in that streptomycin appears capable, under optimal conditions, of bactericidal, in addition to suppressive, action *in vivo*.

Concentration of streptomycin in the blood: Like penicillin, a large percentage of streptomycin is excreted with the urine within a relatively short time after parenteral administration. On the day the long-term experiment was terminated each of the 23 guinea pigs received a final dose of 1,500 units of strepto-

mycin subcutaneously. The final dose of streptomycin was given at least six hours subsequent to the previous dose. The time schedule for the injection of streptomycin into the respective animals was arranged so that specimens of blood for streptomycin assay representing different intervals of time after the last dose of streptomycin would be available.

The animals were anesthetized with chloroform and specimens of blood were obtained by cardiac puncture. The specimens of blood were submitted to the laboratory of our colleague Dr. Dorothy Heilman¹⁸ who made the assays for streptomycin content.¹⁹ The results of Doctor Heilman's tests may be summarized as follows: Blood obtained from 5 guinea pigs one hour to one and a half hours after injection of streptomycin contained not less than 3.12 units of streptomycin per cc. and one specimen assayed 4.68 units per cc. In blood taken from 8 guinea pigs killed at intervals of one hour and forty minutes up to two and a half hours after the last dose of streptomycin, the streptomycin content of 6 was 1.56 units per cc., in one it was 3.12 units per cc. and in one no streptomycin was detected. In blood from the remaining 10 guinea pigs obtained at intervals from two hours and fifty minutes to as long as six hours after the last dose of streptomycin the method of assay failed to detect streptomycin.

These data, although not comprehensive, supply a sufficient reason for the rather frequent administration of streptomycin if a detectable blood concentration of the drug is to be maintained. Unless incorporated into a suitable menstruum that would slow the absorption of the substance, the optimal time schedule for administering streptomycin to guinea pigs would appear to be every three hours.

Toxicity of streptomycin: We have been impressed with the fact that the streptomycin supplied for our third experiment was tolerated with fewer undesirable side reactions than was true of the material originally obtained from Doctor Waksman. Improved methods of preparation have resulted, we are sure, in a more purified and less toxic product. It is doubtful that the streptomycin utilized in these studies was of sufficient purity to permit the formation of a clear opinion of the toxic properties of the active ingredient.

The toxicity of the preparation supplied for our third experiment was apparently of a low order. As evidence of its failure to induce irreversible deleterious reactions is the fact that the animals in the treated group in our third experiment received the drug four times daily continuously for 166 days. During this period no deaths that could be ascribed to the toxic effects of streptomycin occurred among the group of 25. The animals ate well, continued to be in apparently excellent health and experienced a satisfactory weight and growth curve (figure 13). The average weight of the 25 animals when treatment was started was slightly less than 700 g. One hundred and sixty-six days later the average weight of the 23 animals that survived the period of observation was in

¹⁸ The Division of Clinical Pathology, Mayo Clinic, Rochester, Minnesota.

¹⁹ The method of assay used by Doctor Heilman embraces the slide-cell procedure. A description of the method was published recently (15).

excess of 950 g.²⁰ In spite of the long period of therapy, in none of the animals in our third experiment did increased intolerance or sensitivity develop. It is possible that administration of streptomycin in the dose used (6,000 units daily) could have been continued indefinitely.

As further evidence of the low toxicity of streptomycin are the observations of our colleague Dr. Dorothy H. Heilman, who studied the cytotoxicity of streptomycin by a method described by Herrell, Heilman and Gage (16) for determining the toxicity of bactericidal agents.²¹ Doctor Heilman's observations were made on nine different lots of streptomycin hydrochloride, furnished

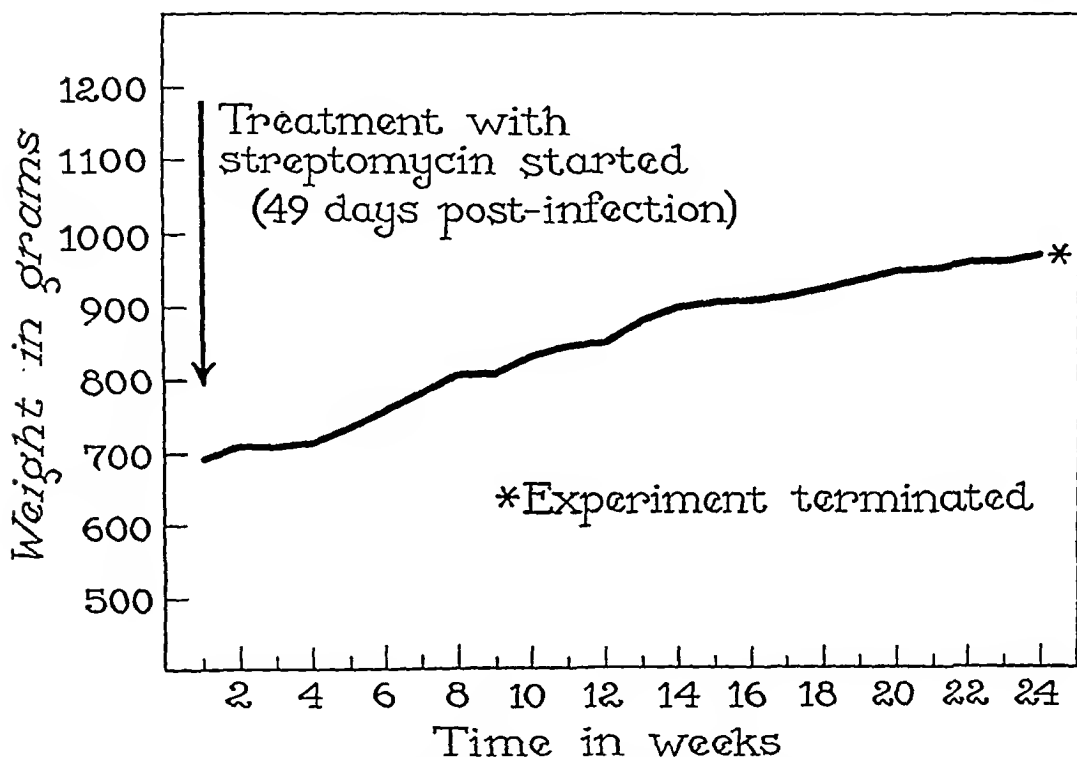


FIG. 13. The gradual and continuous increase in average weight of the animals treated daily with streptomycin for 166 days.

through the kindness of Dr. D. F. Robertson, Merck and Company, Rahway, New Jersey. She summarized her results as follows: "In a concentration of 1:2,000 most of the samples showed a slight decrease in migration of macrophages or a moderate inhibition of fibroblastic growth or both. In a concentra-

²⁰ The weight curve was constructed from data obtained by weighing the animals twice weekly.

²¹ In testing the cytotoxicity of streptomycin by the method of Herrell, Heilman and Gage, the procedure was essentially as follows: Suitable dilutions of the samples of streptomycin hydrochloride were made in Tyrode's solution and added to Carrel flask cultures of explants of normal rabbit spleen. A similar volume of Tyrode's solution was added to control cultures. Measurements were made of the migration of macrophages on the fourth day and fibroblastic growth measurements were made on the sixth day of incubation.

tion of 1:4,000 migration and growth of cells were as extensive as in the control cultures in every instance. Between streptomycin and penicillin on the basis of weight, the two substances appear to be of the same order of toxicity. The cytotoxicity of streptomycin as well as that of penicillin is low compared with that of other bactericidal agents."

As mentioned previously, blood was obtained from animals in both the treated and untreated groups when the third experiment was terminated. The respective blood specimens were subjected to hematological study by our colleague, Dr. George M. Higgins. The blood specimens studied represented a total of 24 guinea pigs. Six were from the group of untreated controls and 18 were animals

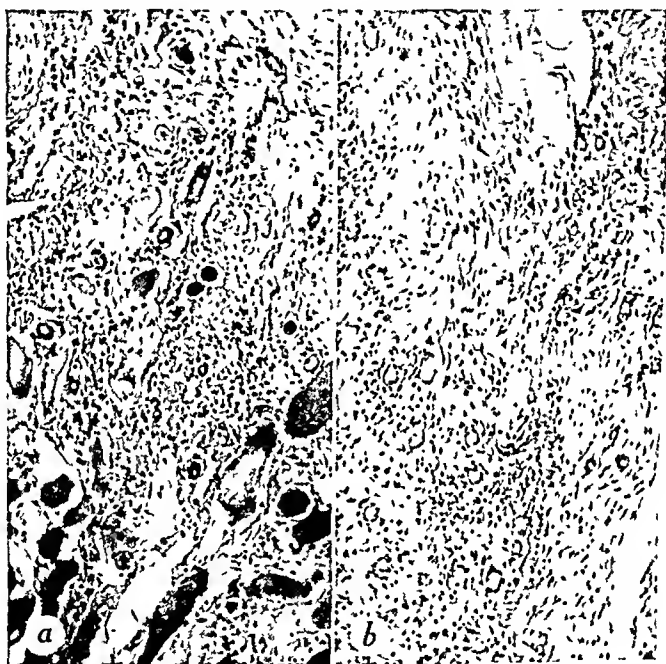


FIG. 14. Tissue changes in axillary space of 2 guinea pigs after many injections of streptomycin over a period of 166 days. *a*. Area of granulation tissue replacing atrophic muscle ($\times 130$). *b*. Compact connective tissue with many small vascular channels ($\times 130$).

that had received streptomycin daily for 166 days. Data were obtained concerning the erythrocytes, hemoglobin and the leucocytes and Doctor Higgins concluded that the data from the treated and untreated groups of animals were statistically identical and were within the normal range.

Local cellular reactions: The fact that streptomycin was injected subcutaneously into the animals in our third experiment for a rather protracted period provided an unusual opportunity to study the local cellular reaction to the drug. The majority of the injections were made into the soft tissues of the right and left axillary spaces. At necropsy tissue from the left axillary space of all treated animals was preserved for subsequent study. Since none of the treated animals died after receiving streptomycin for a few days or a few weeks, material showing the early cellular reactions to the local injection of streptomycin is not available. The material studied has been that from animals treated for 166 days. In

most instances the cellular reactions were limited to the soft areolar tissues. These had been replaced by fibrous connective tissue of variable cellularity (figure 14). In some areas the reaction was rather collagenous while other areas were characterized by numerous and apparently immature fibroblasts. In some instances a few foreign body giant cells were present. Acidophilic granulocytes were commonly present as were histiocytic forms. Small vascular channels were frequently a prominent feature of the fibroblastic reaction. Occasionally small abscesses were noted. In a few instances there was considerable recent hemorrhage but edema was missing or scant. While the reactions for the most part occurred in, and were limited to, the loose alveolar tissue of the axillary space, occasionally the reactive process involved the portions of the contiguous muscle (figure 14). Generally speaking, the local cellular reaction to repeated injections of streptomycin was that of a granulomatous response. What part infections may have had in the cellular reaction is problematic. The skin overlying the sites of injection was not disinfected prior to the introduction of the hypodermic needle and infection from this source is likely.

Our impressions regarding the toxicity of streptomycin suggest that this substance has little inherent toxicity. Toxic manifestations when they occur should, we believe, be attributed to factors not related to streptomycin *per se*. The most efficient methods utilized at the present time in preparing streptomycin do not exclude extraneous material and such material may well be the source of toxic effects charged to the antibiotic substance.²²

Strain susceptibility or resistance: It will be recalled that two different strains of *Mycobacterium tuberculosis* were used to prepare the infective inoculums used in experiments 2 and 3. One was strain H37RV, which has been extensively used in studies of experimental tuberculosis for many years.²³ The other strain used was a subculture of a strain which we had isolated a few months previously from a man affected with far advanced and progressive pulmonary tuberculosis. In both experiments some of the animals in both the treated and untreated groups were inoculated with one strain and the rest of the animals with the other. The results indicated quite definitely that streptomycin was equally effective against the two strains.²⁴

COMMENT

Since the report of Rich and Follis (18) in 1938 on the deterrent effect of sulfanilamide on *Mycobacterium tuberculosis in vivo*, the question of chemotherapy in

²² Further studies are being made utilizing higher doses and later it is anticipated that more highly purified products will be obtainable.

²³ The virulence of subcultures of strain H37RV obtained from several different laboratories was studied by Corper and Cohn (17). The results indicated a wide divergence of virulence of different subcultures of this organism. Our subculture was among those included in Corper and Cohn's study and was found at that time (1943) to be but slightly less virulent than the most virulent of the subcultures studied.

²⁴ Another and more extensive study designed to determine possible differences in sensitivity to streptomycin of several strains of freshly isolated cultures of *Mycobacterium tuberculosis* is now being done.

tuberculosis has been reopened. What previously had seemed to be an impenetrable problem and one invulnerable to specific attack by chemical agents now appeared assailable. There followed an impressive array of experimental trials with a long list of sulfonamide compounds in the search for a substance that would effectively control tuberculosis in the experimentally infected guinea pig but the results were rather unrewarding.

The first significant break in the formidable armor of *Mycobacterium tuberculosis* came with the advent of a derivative of 4,4'-diaminodiphenyl sulfone. The successful derivative was sodium p,p'-diaminodiphenylsulfone-N,N'-dixetrose sulfonate, designated by the trade name promin. With this sulfone compound it was possible for the first time to achieve a striking deterrent effect on well established tuberculosis in the highly susceptible guinea pig (19, 20). However, the efficacy of promin in experimental tuberculosis was not absolute. The infection could be kept indefinitely in a state of suppression so long as the medication was continued but when medication was stopped the treated animals would eventually succumb to their tuberculous disease (21, 22). Clinically, promin was not a desirable drug because of a high toxic potential for certain hematopoietic elements.

The search for more effective and less toxic sulfone compounds continued and disodium formaldehyde sulfoxylate diaminodiphenyl sulfone (diasone) was synthesized. The tuberculochemotherapeutic properties of diasone for experimental tuberculosis were found to be fairly comparable to those of promin (23, 24). However, the toxicity of diasone constituted a serious obstacle to its general acceptance for clinical use. The next substance that proved promising on the basis of experimental data was 4,2'-diaminophenyl-5'-thiazolyl sulfone (promizole). This drug was as effective as promin in its favorable influence on well established experimental tuberculosis in guinea pigs (25). Furthermore, it had the desirable virtue of being less toxic for human beings than any of the other sulfones that had appeared so promising as a result of experimental trials in guinea pigs. Clinically, however, promizole has proved disappointing for reasons not as yet well understood (26).

The discovery and subsequent development of penicillin provided a highly effective and practically nontoxic chemotherapeutic agent. It was logically hoped that penicillin would be useful against tuberculosis. Unfortunately, experimental trials showed this antibiotic to offer little, if any, promise in combating this disease (27 to 31). The observation of Schatz and Waksman that streptomycin has the ability to exert a bacteriostatic and bactericidal action *in vitro* on a human strain of *Mycobacterium tuberculosis* and our own studies on the effect of streptomycin *in vivo* against tuberculous infections suggest very definitely the potentialities of antibiotics in the experimental attack on infections due to *Mycobacterium tuberculosis*. The relatively low toxicity for guinea pigs of the more purified product makes it possible to administer streptomycin in therapeutically adequate doses to these animals for prolonged periods without deleterious effects. Of great importance is the fact that, unlike most of the sulfone compounds found to be effective in combating experimental tuberculosis, streptomycin apparently does not produce in guinea pigs a recognizable blood dyscrasia.

As brought out in the experimental data, streptomycin exerted a striking inhibitory action on the *in vivo* activities of *Mycobacterium tuberculosis* but did not succeed in eliminating or in killing all of the infective agents in the animals constituting our experiments. As we have indicated elsewhere (11), one of the critical requirements that should be demanded of a substance having anti-tuberculosis effects in experimental tuberculosis in guinea pigs is the ability of the drug to eliminate or to render avirulent *Mycobacterium tuberculosis* in the organs of predilection. This may or may not be a reasonable requirement for any chemotherapeutic substance to meet. However, failure of a drug to meet this requirement may indicate (1) that the substance has a limited potential effectiveness, (2) that the dose is inadequate, (3) that the drug should be administered more frequently or by a different route or (4) that the duration of treatment should be extended. Although streptomycin did not meet this requirement in all instances, the fact that tuberculosis failed to develop in normal guinea pigs inoculated with suspensions prepared from the spleens of 8 treated animals appears significant. A careful consideration of the various factors of this phase of the study appears to justify the impression that streptomycin did induce a considerable reduction of the infective bacteria and it is possible that more of the microorganisms would have been eliminated by a more intensive and prolonged treatment.

The dosage schedules followed in our studies probably do not represent the optimal. So far as we know, the upper limits of tolerance of guinea pigs for streptomycin have not been determined. It is our belief that, with a product of maximal purity, medication of guinea pigs with streptomycin could be continued indefinitely.

A factor that may well have militated against the maximal therapeutic effects from streptomycin in our studies was the relatively long interval between successive injections of the drug. As mentioned previously, streptomycin, like penicillin, is excreted rather rapidly from the body following parenteral administration and this fact should be carefully considered when maximal therapeutic effects are anticipated. The results of the studies to determine the concentration of streptomycin in the blood of the animals treated in our third experiment demonstrated very clearly that administration of the drug every six hours was not frequent enough to maintain a detectable blood concentration by the method used. As a matter of fact, if it is assumed that detectable amounts of streptomycin given parenterally can no longer be demonstrated after two and a half to three hours, then the treated animals in our third or long-term experiment were devoid of the drug during about one-half of each twenty-four hours. Whether or not intermittent therapy of experimental tuberculosis with streptomycin will give results comparable to a situation where detectable amounts of the substance are present continuously in the blood is not known. However, until facts to the contrary are available it would seem logical to expect the maximal results from the administration of the substance in adequate amounts and sufficiently frequently to insure the maintenance at all times of a therapeutically suitable blood concentration. What value constitutes a therapeutically adequate blood concentration of streptomycin is yet to be established.

The results of these experiments with streptomycin seem to indicate that this substance is the most effective *in vivo* tuberculochemotherapeutic agent which we have studied or which we have seen reported in the literature. The relatively low toxicity for guinea pigs of the more purified product and its high efficacy in resolving and suppressing what would otherwise be lethal tuberculosis in guinea pigs establish streptomycin as an antibiotic worthy of serious consideration and of further study.

Clinical considerations: It has been repeatedly demonstrated that antibacterial substances which are active against *Mycobacterium tuberculosis in vitro* may be of little or no value in combating the infection in experimental animals and in human beings. It should again be emphasized that tuberculosis experimentally induced in guinea pigs offers many contrasts to the disease which the same organism produces in man. Also, it may be stated that the tubercle bacillus produces several dissimilar types of disease in man, so different as to be essentially distinct diseases. In all of the common tuberculous diseases of man the pathological alterations produced are much more complex than those in the animals studied at the time treatment was begun in this series of experiments. Any effort to predict what streptomycin may accomplish for human tuberculosis enters into the uncertain field of speculation.

Serious harm may result to patients who refuse such proved remedies as sanatorium care and collapse therapy, in the remote hope that a powerful chemotherapeutic remedy is imminent. We must emphasize to physicians and patients that prolonged and difficult studies must yet be carried out before any estimate can be attempted of the clinical potentialities of streptomycin.

We have been hesitant to publish these experimental findings because of the fear that unwarranted clinical implications might be expressed by those who are not familiar with the many previous therapeutic disappointments in the history of tuberculosis. However, the laboratory investigator also has the important responsibility of promptly recording those results which may be of value to other investigators and it is hoped that this record of the first successful use of a modern antibiotic agent in experimental tuberculosis will stimulate interest and direct research activity to this promising field of study.

SUMMARY AND CONCLUSIONS

Three experiments are described which demonstrated the ability of the antibiotic, streptomycin, to control experimental tuberculosis successfully in guinea pigs. Two of the experiments were of short duration while the third continued for a period of 215 days. Two strains of *Mycobacterium tuberculosis* were used; both were of the human variety. The drug was administered subcutaneously four to six times daily. The first two, or preliminary, experiments having yielded impressive results, the third or crucial *in vivo* study was done. In the latter, guinea pigs were inoculated with *Mycobacterium tuberculosis* forty-eight days before treatment was started. The day before treatment began, biopsy of the liver was done on all the animals. This was to provide information on the state of the infection prior to treatment, which could be compared with the situa-

tion in the same respective livers at the end of the treatment period. The animals received 6,000 units of streptomycin daily, divided into four equal doses. The treated group consisted of 25 guinea pigs, while the group of untreated controls totaled 24 animals. When the experiment was terminated after 166 days of treatment, 17 (approximately 70 per cent) of the untreated animals had died, compared to 2 (8 per cent) of the group that had received streptomycin. Nearly all of the untreated controls showed at necropsy severe, widely disseminated tuberculosis while the tuberculous disease among the animals that had been treated was minimal. Thirteen (52 per cent) of the treated animals had no tuberculosis grossly or microscopically. Nine (approximately 39 per cent) of the treated animals living when the experiment was terminated gave a negative reaction to tuberculin. The following conclusions are drawn:

1. The antibiotic, streptomycin, under the conditions imposed was effective in resolving or suppressing established experimental tuberculous infections in guinea pigs.

2. Streptomycin preparations used had a low toxicity for guinea pigs in doses of 6,000 units per day and were tolerated without recognizable deleterious effects for a prolonged period.

3. Although capable of striking deterrent effects in combating or preventing anatomical changes due to *Mycobacterium tuberculosis*, streptomycin in most instances exerted a suppressive rather than a sterilizing effect on the infective agent.

4. In some instances (approximately 39 per cent) successful treatment with streptomycin resulted in a reversal of a positive to a negative sensitivity to tuberculin.

5. Larger doses and more frequent administration of streptomycin might have enhanced the bacteriostatic effects.

6. The striking effects of streptomycin in reversing a potentially lethal tuberculosis in the highly susceptible guinea pig and the low toxicity and corresponding safety of purified streptomycin are prerequisites of a drug worthy of limited clinical trial when adequate supplies become available and its pharmacological properties have been studied in man.

7. Any conjecture as to the clinical potentialities of streptomycin appears to be very unwise at this time.

SUMARIO Y CONCLUSIONES

Describense tres experimentos en que se demostró la capacidad del anti-biótico estreptomicina para cohibir la tuberculosis experimental en el cobayo. Dos de los experimentos duraron poco tiempo, pero el tercero continuó por espacio de 215 días. Utilizáronse dos cepas de *Mycobacterium tuberculosis*, ambas de la variedad humana. La droga se administró subcutáneamente de cuatro a seis veces diarias. Habiendo dado los primeros dos experimentos, los preliminares, resultados imponentes, se llevó a cabo el tercer estudio, el crítico, *in vivo*. En este último se inoculó a los cobayos *Mycobacterium tuberculosis* 48 días antes de iniciar el tratamiento. El día antes de iniciarlo se ejecutó una

biopsia hepática en todos los animales, a fin de obtener información relativa al estado de la infección antes del tratamiento y poder compararlo con la situación en los mismos hígados respectivos al terminar el período terapéutico. Los animales recibieron 6,000 unidades diarias de estreptomycin divididas en cuatro dosis iguales. El grupo tratado constaba de 25 cobayos y el de testigos de 24. Al terminar el experimento, al cabo de 166 días de tratamiento, habían muerto 17 (aproximadamente 70 %) de los animales no tratados, comparado con 2 (8 %) en el grupo que recibió estreptomycin. Casi todos los testigos no tratados revelaron en la autopsia una grave tuberculosis muy diseminada en tanto que era mínima la afección tuberculosa entre los animales tratados. Trece (52 %) de los animales tratados no mostraron tuberculosis macro o microscópica. Nueve (aproximadamente 23 %) de los animales tratados que vivían al terminar el experimento acusaron una reacción negativa a la tuberculina. Del estudio sacáronse las siguientes conclusiones:

1. El antibiótico, estreptomycin, en las condiciones impuestas resultó eficaz para resolver o suprimir infecciones tuberculosas experimentales establecidas en el cobayo.

2. Las preparaciones de estreptomycin utilizadas mostraron poca toxicidad para el cobayo a la dosis de 6,000 unidades por día y fueron toleradas durante un período prolongado sin producir efectos nocivos reconocibles.

3. Aunque capaz de producir notables efectos en lo relativo a combatir o impedir las alteraciones anatómicas debidas al *Mycobacterium tuberculosis*, la estreptomycin en la mayor parte de los casos ejerció efecto supresor más bien que esterilizante sobre el agente infectivo.

6. En algunos casos (aproximadamente 39%) el tratamiento con la estreptomycin hizo virar a negativa una reacción positiva a la tuberculina.

5. Dosis mayores y una administración más frecuente de la estreptomycin tal vez hubieran acrecentado el efecto bacteriostático.

6. Los notables efectos de la estreptomycin para modificar una tuberculosis potencialmente letal en el susceptible cobayo y la baja toxicidad y correspondiente inocuidad de la estreptomycin purificada son condiciones que debe cumplir una droga acreedora a limitadas pruebas clínicas, cuando haya a mano abastos adecuados y se hayan estudiado en el hombre sus propiedades farmacológicas.

7. Toda conjetura acerca de las potencialidades clínicas de la estreptomycin parece ser muy imprudente por ahora.

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STREPTOTHRICIN IN EXPERIMENTAL TUBERCULOSIS

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Streptothricin, the antibiotic substance obtained from *Actinomyces lavendulae* by Waksman and Woodruff (1), was made available to use for *in vivo* tests against human tubercle bacilli in July, 1944.³ Previously the microbiologic aspects of this substance had been studied by Woodruff and Foster (2, 3). Studies to determine toxicity for mice and *in vivo* activity of streptothricin against *Salmonella Schottmülleri*, *Salmonella aertrycke*, *Escherichia coli* and *Shigella dysenteriae* were reported by Robinson, Graessle and Smith (4). They concluded that although crude streptothricin was markedly effective *in vitro* against many gram-positive and gram-negative organisms, certain gram-negative and most gram-positive species were quite resistant to the action of streptothricin *in vivo*. Robinson, Graessle and Smith established that body fluids had no apparent inhibitory effect on the action of streptothricin and that mice tolerated single doses of 30,000 units per kilogram administered intravenously or subcutaneously without evidence of toxicity during a five-day period of observation.

Woodruff and Foster (5) studied the inhibition *in vitro* of several species of mycobacteria by streptothricin. The organisms studied were *Mycobacterium tuberculosis hominis*, *Mycobacterium tuberculosis avium*, *Mycobacterium leprae* and two strains of *Mycobacterium smegmatis*. It was found that mycobacteria exposed to streptothricin in Long's medium were among the most sensitive of the organisms tested to this antibiotic. In addition to a considerable inhibitory action Woodruff and Foster presented data suggesting the bactericidal activity of streptothricin against mycobacteria. They expressed the belief that the results of their *in vitro* experiments suggested the desirability of determining the effects that streptothricin might have in influencing experimental tuberculosis in animals.

METHODS

Each of 20 male guinea pigs having an average weight of 520 g. was inoculated subcutaneously with a suspension containing 0.1 mg. of human tubercle bacilli. Ten of the animals received strain H37RV and 10 received a strain of human tubercle bacilli isolated a few months previously from a patient who had progressive pulmonary tuberculosis (strain 3728). The animals were divided into two groups: group A, which was not to receive treatment and was to serve as control; and group B, which was to be treated with streptothricin. One-half of the animals in group A had been inoculated with H37RV strain of tubercle bacilli and the rest had been inoculated with strain 3728. In group B one-half

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³ The substance was supplied as streptothricin hydrochloride by Merck and Company, Rahway, New Jersey.

of the animals had been inoculated with strain H37RV and one-half with strain 3728.

Treatment of 6 of the infected animals with streptothricin was started on the day of inoculation. In 4, treatment was delayed until the lapse of two weeks after inoculation. The streptothricin was administered subcutaneously every six hours. The amount given at each injection was 875 units,⁴ totaling 3,500 units daily. However, after 15 injections, during which time the animals each received a total of 13,125 units of streptothricin, there were unmistakable signs of toxicity and treatment was discontinued for two days. During this interval each of the 6 animals that had been receiving streptothricin had lost weight and 3 had died. Since the dose selected previously was not tolerated satisfactorily, the subsequent daily dose of streptothricin was reduced to 1,750 units per animal, given, as mentioned before, in four divided doses six hours apart.

RESULTS

Toxicity: Even the reduced dose of streptothricin (1,750 units) was tolerated rather poorly by the infected guinea pigs. Each animal experienced a loss of weight, which varied from a minimal loss of 80 g. to a maximal loss of 200 g. The other signs of toxicity were sluggish behavior, hematuria and edema of the external genitalia, incontinence and in some instances a bloody discharge from the rectum with prolapse. Microscopically among those animals that died early in the experiment there were severe morphological derangements of the liver suggesting regions of focal necrosis with a circulatory basis of origin. Several of the animals showed bilateral pyelitis and a marked edematous thickening of the wall of the urinary bladder especially associated with the tissues lying immediately beneath the mucosa. In some the vesical mucosa was eroded in small areas and the mucosal structure was packed throughout its depth with erythrocytes. This suggested the explanation for the hematuria. Parenchymal damage to the kidneys was not observed.

The failure of the animals to tolerate streptothricin satisfactorily under the conditions imposed is evident from the large percentage of the treated animals that died. When the experiment was terminated sixty-one days after the animals had been inoculated with tubercle bacilli, only 3 of the 10 animals that received streptothricin were living. During the same period, of the 10 untreated controls only one had died.⁵

Antituberculosis effects: Of the 7 guinea pigs that survived more than eight days after treatment was started, the amount of tuberculosis noted at necropsy was recorded as moderate to severe (figure 1). The 3 animals that were still

⁴ A unit of streptothricin has been defined by Robinson, Graessle and Smith (4) as the "minimum quantity of drug which when added to 1.0 cc. of nutrient broth will inhibit a given strain of *E. coli*."

⁵ At the time when the effect of streptothricin on experimental tuberculosis was being studied there was conducted concurrently a study of streptomycin on experimental tuberculosis. During the sixty-one day period of observation only one of the 10 animals treated with streptomycin died (6).

living in the delayed treatment group when the experiment was completed had severe tuberculosis comparable to that which characterized the disease in the untreated controls. The longest period during which any of the animals was treated with streptothricin was forty-seven days and neither grossly nor microscopically was there any evidence that treatment with streptothricin had exerted a favorable influence on the course of the disease.⁶

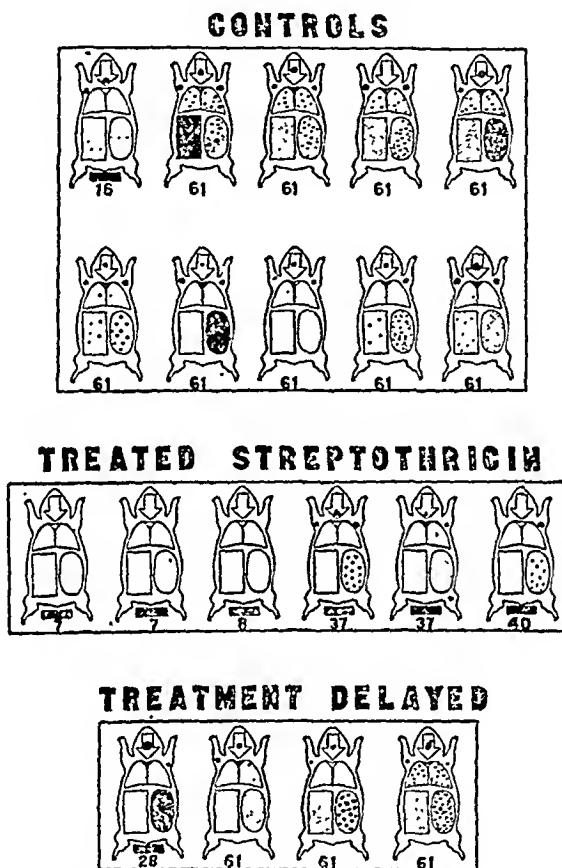


FIG. 1. Amount and distribution of tuberculous lesions recorded schematically at the time of necropsy. The respective numerals indicate the number of days after inoculation before death. The black bar above a numeral indicates that the animal died. The animals represented by the top group were not treated. Treatment of the middle group with streptothricin was started the day the animals were inoculated with tubercle bacilli. In the group represented at the bottom, treatment was delayed until the lapse of two weeks after inoculation. For further explanation of symbols used see figure 1 of AM. REV. TUBERC., 1945, 61, 582.

COMMENT

Many substances of both natural and synthetic origin possess the ability to suppress the growth of *Mycobacterium tuberculosis* *in vitro*. Very few of these

⁶ The failure to observe results of therapeutic efficacy with streptothricin was in marked contrast to the strikingly favorable results obtained under similar experimental conditions with streptomycin (6).

retain such power when tested against the disease, tuberculosis, in experimental animals. The first modern antibiotic substance found to have effective therapeutic properties against experimental tuberculosis is streptomycin; hence, it is of unusual interest and significance to learn that a substance of similar origin and with similar bacteriostatic properties *in vitro* should prove to be ineffective *in vivo*. This fact emphasizes the necessity for animal experimentation in evaluation of antibiotic substances as well as in evaluation of synthetic antibacterial substances.

SUMMARY AND CONCLUSIONS

Streptothricin was tested for its ability to influence the expected course of experimental tuberculosis in guinea pigs. The antibiotic was administered subcutaneously and the daily dose was divided into four equal amounts and injected at six-hour intervals. The following conclusions were drawn:

1. The streptothricin available and in the dose used was poorly tolerated by rather large, previously vigorous guinea pigs. All but 3 of the 10 guinea pigs treated with streptothricin died during sixty-one days of observation.

2. Unlike streptomycin, another antibiotic also obtained from a species of *Actinomyces* and which has a high therapeutic potential in tuberculosis of guinea pigs, streptothricin under the conditions described proved devoid of demonstrable deterrent qualities that would suggest antituberculosis effects.

SUMARIO Y CONCLUSIONES

La estreptotricina fué comprobada con respecto a su capacidad para modificar la evolución anticipada de la tuberculosis experimental en el cobayo. El antibiótico fué administrado subcutáneamente, dividiéndose la dosis diaria en cuatro fracciones iguales e inyectándose a plazos de seis horas. Sacáronse las siguientes conclusiones:

1. La estreptotricina disponible a la dosis utilizada fué mal tolerada por cobayos algo grandes y previamente vigorosos, muriendo 7 de los 10 tratados durante los 61 días de observación.

2. En contraposición a la estreptomicina, otro antibiótico obtenido de una especie de *Actinomyces* que mostró un alto potencial terapéutico en la tuberculosis del cobayo, la estreptotricina en las condiciones descritas no reveló propiedades cohibidoras que indicaran acción antituberculosa.

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CHEMOTHERAPY OF SULFONES AND SULFONAMIDES IN EXPERIMENTAL TUBERCULOSIS¹

Further Studies

M. I. SMITH AND W. T. McCLOSKEY

In a survey of the action of a series of sulfonamides, sulfones and certain phosphorus related compounds in experimental tuberculosis it was shown in 1942 that little could be expected from the sulfonamides and that the sulfones appeared to hold out more promise. Of the sulfonamides studied at that time only sulfadiazine seemed to have a somewhat favorable effect (1). In a later study (2) with a larger group of derivatives of 4-4'-diaminodiphenylsulfone the results indicated but little chemotherapeutic effectiveness in the sodium formaldehyde sulfoxylate derivative (diasone), while the N-phosphoryl derivative synthesized in this laboratory (3, 4) appeared to be the most effective. In the course of the investigations on the phosphorylation of the sulfone another phosphorylated derivative was obtained, a tri-diamido-phosphoric acid derivative (4); the present report deals with the chemotherapeutic effectiveness of this compound in experimental tuberculosis.

For comparative purposes experiments were made simultaneously with the parent substance 4-4'-diaminodiphenylsulfone as the standard of reference and another sulfone derivative, promizole, which had previously been reported to be effective in experimental tuberculosis by Feldman and associates (5). In addition, experiments were carried out at the same time with three sulfonamides hitherto untried, namely, P-n-caproylaminobenzenesulfonhydroxamide (sulfabenamide), N'-dimethylacrylsulfanilamide (irgamide) and N'-3,4-dimethylbenzoxysulfanilamide (irgafen). Sulfabenamide had previously been found to be effective in experimental streptococcus infection in rabbits (6), and irgamide was reported to be effective in experimental pneumococcal and streptococcal infections in mice (7). Little information is available on irgafen. Irgamide and irgafen were supplied by the J. R. Geigy Company, sulfabenamide by Sharp and Dohme, Inc. and promizole by Parke, Davis & Company.

One hundred and forty male guinea pigs of from 250 to 350 g. each were inoculated intraperitoneally with a 1 cc. suspension of tubercle bacilli A27 human strain, representing approximately 1 mg. of bacilli moist weight. The animals were divided into seven groups, 20 each, and treated as follows:

1. *Group A* received daily 0.1 to 0.2 g. per kg., usually 0.15 g. per kg., 4-4'-diaminodiphenylsulfone as a 5 per cent solution in propylene glycol.
2. *Group B* received daily 0.5 g. per kg. tri-diamidophosphoric acid derivative of the sulfone as a 10 per cent solution in propylene glycol containing 10 per cent water.
3. *Group C*—controls.

¹ From the Division of Physiology, National Institute of Health, U. S. Public Health Service, Bethesda, Maryland.

4. *Group D* received daily 0.5 g. per kg. promizole as a 10 per cent aqueous suspension in 5 per cent gum acacia. Early signs of toxicity necessitated reduction of dosage at intervals to 0.4 or even 0.3 g. per kg.
5. *Group E* received 0.3 to 0.5 g. per kg. sulfabenamide in aqueous suspension as above.
6. *Group F* treated daily with 0.5 g. per kg. irgamide in the same manner.
7. *Group G* treated daily with 0.5 g. per kg. irgafen suspension as above.

Treatment was begun the day following infection and was continued for a period of forty days. All drugs were administered by stomach tube connected with a graduated syringe; the treatment was given once daily except Sundays with no change in dosage except in the animals of groups A, D and E, in which dosage had to be reduced frequently on account of drug toxicity as manifested

TABLE 1
Blood levels at the end of the experimental period
Average of 6 animals

GROUP AND DRUG	BLOOD CONCENTRATION, MG. PER CENT*					
	4 hours		6 hours		24 hours	
	Free	Total	Free	Total	Free	Total
A. 4-4'-diaminodiphenylsulfone.....	7.9	7.6	5.9	6.1	1.0	—
B. Tridiamido phosphoric acid derivative.....	2.2	—	2.2	—	trace	trace
D. Promizole.....	17.3	17.2	15.1	—	3.0	3.1
E. Sulfabenamide†.....	8.5	13.8	8.0	13.8	2.3	5.9
F. Irgamide.....	22.2	26.2	16.9	20.9	3.2	4.5
G. Irgafen.....	16.0	23.1	11.7	22.4	2.3	5.0

* Method of Bratton and Marshall (8).

† All determinations made against the acid hydrolyzed standard. The results indicate that the compound hydrolyzes in the body fairly rapidly and quite completely and it would appear that acetylation may follow this.

by excessive loss of weight. The plan of the experiment was to administer the drugs up to the limits of tolerance, but not to exceed 0.5 g. per kg. The limits of tolerance of the parent sulfone in guinea pigs when given repeatedly is in the neighborhood of 0.15 g. per kg. (2). Promizole and sulfabenamide were tolerated in doses of 0.5 g. per kg. for a while, but dosage had to be reduced at intervals to 0.3 or 0.4 g. per kg. Even under these conditions several animals were lost inadvertently from drug toxicity.

The relative toxicity of the drugs used and the blood levels that could be maintained under the experimental conditions are shown in chart 1 and table 1, which represent the data obtained in groups of normal guinea pigs, 6 each, treated once daily in the dosage indicated for a period of thirty days. Blood

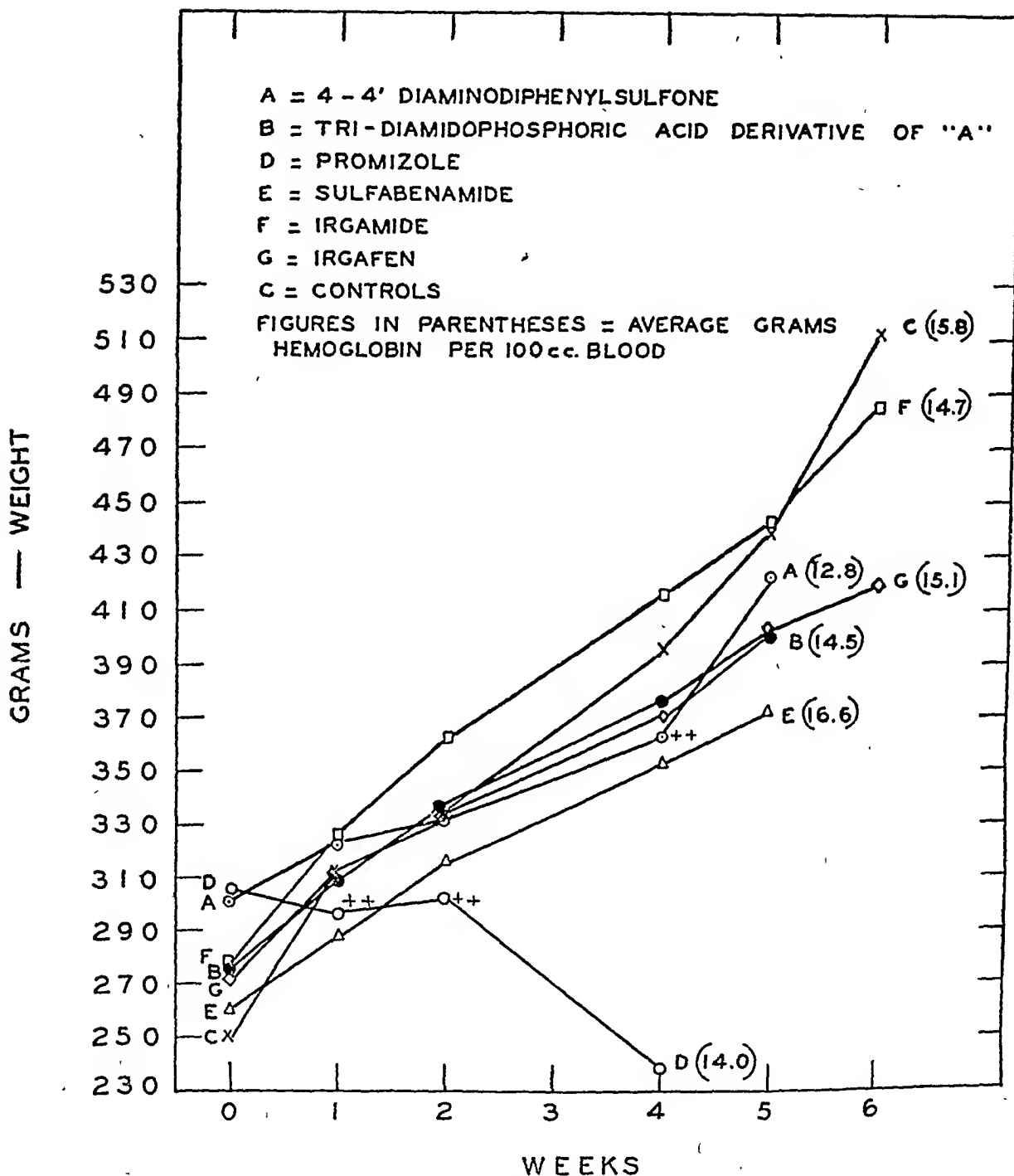


CHART 1. Toxicity of the several drugs in normal guinea pigs. 4-4'-diaminodiphenylsulfone administered once daily at a dosage level of 0.15 g. per kg.; all others at 0.5 g. per kg. The sign + indicates death of an animal. Under the experimental conditions 4 animals died in the promizole group and 2 in the diaminodiphenylsulfone group. These animals were replaced in order to maintain 6 animals in each group to the end of the experiment.

level determinations were made at the termination of the experiment. As may be seen in chart 1, promizole was the most toxic, diaminodiphenylsulfone at a

dosage level of a little less than one-third was next in order, while the tridiamido derivative, irgamide and irgafen were the least toxic. Of the three sulfones, promizole produced the highest blood levels, diaminodiphenylsulfone next, and the tridiamido derivative gave the lowest blood levels. The low blood levels in the latter instance were due to poor and irregular absorption, since with subcutaneous injections of the drug in aqueous solution it was possible to obtain considerably higher blood levels. The local irritant action of the drug when given subcutaneously in guinea pigs precluded its use in this manner.

TABLE 2

The chemotherapeutic effect of three sulfones and three sulfonamides

GROUP AND DRUG	MORTALITY PER CENT AT 100 DAYS WHEN EXPERI- MENT WAS TERMI- NATED	AVERAGE SURVIVAL IN DAYS AT TER- MINATION OF EX- PERIMENT	AVER- AGE WEIGHT GAIN IN GRAMS	NUMBER LOSING WEIGHT AT TER- MINATION OF EX- PERIMENT	AVERAGE TUBERCULOSIS INDEX		AVERAGE HB. G. PER 100 CC.	
					Animals dying up to 100 days	The whole group	First determi- nation at height of treatment	Second determi- nation before termina- tion of exper- iment
C. Controls.....	45	60	75	8/11	10.0	11.0	14.6	15.2
A. 4-4'-diaminodiphenyl- sulfone.....	45	52	135	3/11	5.5	6.8	12.4	17.0
B. Tridiamido phosphoric acid derivative.....	40	64	85	6/12	4.4	7.5	14.0	16.0
D. Promizole.....	45	64	105	2/11	3.3	7.5	12.4	15.8
E. Sulfabename.....	70	63	29	2/6	6.7	7.4	13.1	14.7
F. Irgamide.....	45	71	122	5/11	9.3	9.8	14.3	15.1
G. Irgafen	40	64	144	5/12	7.7	8.2	15.5	15.6

Hemoglobin determinations at the end of the experimental period showed little effect from any of the drugs used except 4-4'-diaminodiphenylsulfone which had a definite toxic action on the hematopoietic system.

The results of the chemotherapeutic tests are shown in table 2 and chart 2. The extent of tuberculous involvement at necropsy was rated, as previously described (2), on the basis of the gross findings in the groups of tissues and organs most commonly involved: the omentum, the spleen, the liver, the peritoneum kidneys and mesenteric lymph nodes, and the lungs. The extent of tuberculous involvement in each tissue or organ was rated on the basis of 0 to 4, thus giving a possible maximum tuberculosis index of 20. The autopsies and ratings were made for the most part by the same operator throughout the experiment without knowledge of the group to which the animal belonged or the treatment it received.

At one hundred days following inoculation, all the survivors were killed with chloroform and the extent of tuberculous involvement noted. At that time the mortality per cent for the several groups is indicated in the second column of table 2, from which it will be evident that none of the treated animals showed an appreciable advantage over the controls. The mortality rate in the sulfabenzamide group was distinctly higher than in the controls, this being due to drug toxicity. The average survival in days for the several groups at the time the experiment was terminated, shown in the next column, indicates a slight

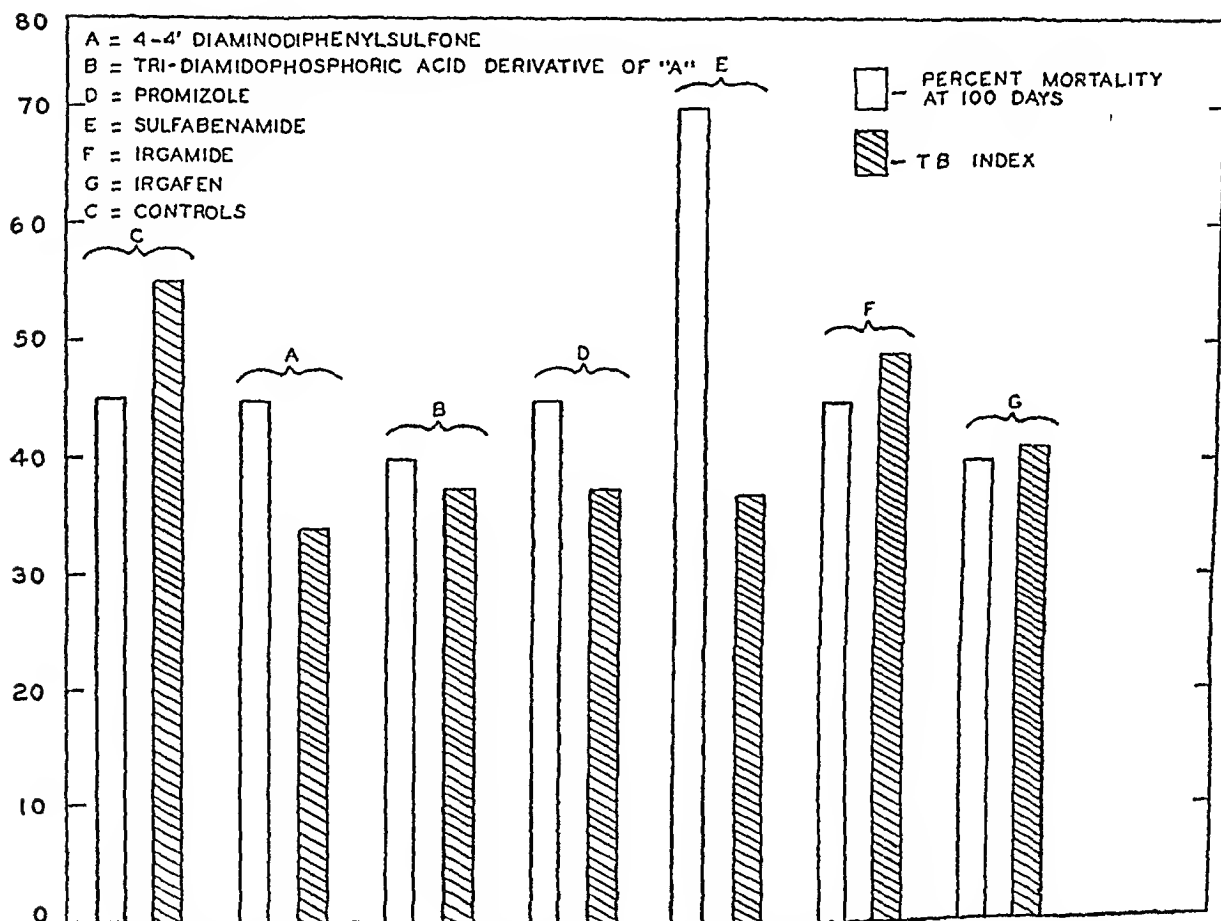


CHART 2. Mortality per cent at the termination of the experiment, and extent of tuberculous involvement as expressed by the average tuberculosis index for each of the treated groups and the control group.

advantage for the irgamide group. The average gain in weight for each group, shown in the next column, indicates an advantage for the diaminodiphenylsulfone, irgamide and irgafen groups over all the others. The number of animals losing weight and definitely on the decline at the termination of the experiment and shown in the next column indicates an advantage for the animals in the diaminodiphenylsulfone group and the promizole group, with the tridiamido derivative and irgamide and irgafen groups about equally balanced. Finally a consideration of the average tuberculosis index for each group as a whole

shows some slight beneficial effect from all the drugs used as compared to the controls, with a definite advantage for the sulfones over the sulfonamides. This is best illustrated in chart 2 which gives the per cent mortality at the time the experiment was terminated and the average tuberculosis index for each of the experimental groups. In the last column of table 2 the average hemoglobin is given, the first determination having been made at the height of treatment, about forty days after inoculation, and the second just before the termination of the experiment at ninety-five to one hundred days. From this it is clear that diaminodiphenylsulfone, promizole and sulfabenamide had a definite toxic action on the hematopoietic system, while little effect was evident from any of the other drugs. The toxic action, however, was reversible, since at the second determination full recovery had been made in most cases.

Consideration of the average tuberculosis index of the animals that died prior to the termination of the experiment as compared with that of the group as a whole leads to the speculation concerning the relative early and late chemotherapeutic effects of the several drugs. It would appear that the effect of diaminodiphenylsulfone was fairly uniform and persistent, while the more marked beneficial effects obtained with the tridiamido derivative and promizole during treatment and during the earlier post-treatment phase of the infection largely disappeared in the surviving animals following a rest period of about two months. It is difficult to make such a comparison for sulfabenamide on account of the high mortality in this group prior to the termination of the experiment. The chemotherapeutic effectiveness of irgamide and irgafen was too slight to attempt such a comparison. In this analysis due consideration was given to the possibility of variations of extent of tuberculous involvement in relation to time of survival, but this was so similar in all the groups, except the irgamide group, that the assumption seems justifiable. Since none of the animals in any of the experimental groups were entirely free of macroscopic tuberculous involvement it may be presumed that the tuberculostatic or attenuating action of diaminodiphenylsulfone was more persistent, though perhaps less marked, than that of the related compounds under consideration. The possibility of attenuating the tubercle bacillus *in vitro* by prolonged cultivation in a medium containing the sulfonated glucose derivative of 4-4'-diaminodiphenylsulfone (promin), in low concentrations, has been demonstrated before (9).

DISCUSSION

The present experiments confirm and extend previous observations reported from this and other laboratories suggesting that the sulfones offer a promising lead in the search for a specific chemotherapeutic agent in the treatment of tuberculosis, while the sulfonamides appear to hold out less promise. In an earlier publication, sulfadiazine appeared to afford a small degree of protection (1). More recently, experiments with sulfamerazine and sulfamethazine failed to show any beneficial effect whatever.² The slightly beneficial effect

² Unpublished data.

obtained in the present experiments with the sulfonamide irgafen would seem to indicate that differences in activity do exist among the sulfonamides too, and it is not inconceivable that substituent groups with more favorable action may be found. There is as yet insufficient information available from which to so correlate chemical constitution and chemotherapeutic action as to rationalize research in this field. It still seems to be largely a matter of trial and error. The generally favorable effects reported so far for sulfone derivatives, including the tridiamido derivative of the present study, appear to be sufficiently encouraging to extend the search for still better compounds of this type. It seems not improbable that better methods of administration or a change in chemical structure to effect better absorption and higher blood levels might yield better results.

The technique adopted in this laboratory for testing the chemotherapeutic effectiveness of new drugs in experimental guinea pig tuberculosis is believed entirely adequate in exploratory work and, in our opinion, research in the chemotherapy of tuberculosis has not yet passed beyond the exploratory stage. The method is not too time-consuming. Intensive treatment with the drug at a level of maximum tolerance during the early phases of a heavy infection may be expected to so retard the tuberculous process as to be readily appraised by gross examination, if the compound has any activity at all. It is only compounds of a high degree of activity, as determined by such preliminary tests, that need be subjected to more elaborate pharmacologic and chemotherapeutic testing prior to clinical trial. It is our opinion that such compounds have yet to be found.

SUMMARY

The chemotherapeutic effectiveness of two sulfones and three sulfonamides was examined in experimental tuberculosis in guinea pigs in comparison with 4-4'-diaminodiphenylsulfone. The two sulfones, the tridiamido phosphoric acid derivative and promizole, showed a degree of retardation of the tuberculous process comparable with diaminodiphenylsulfone. Promizole, however, was the more toxic of the two. Of the three sulfonamides, sulfabenamide was too toxic, irgamide gave little protection and irgafen showed a slightly favorable effect.

SUMARIO

En este trabajo estúdiase la eficacia quimioterapéutica de dos sulfonas y tres sulfonamidos en la tuberculosis experimental en el cobayo, comparándolos con la 4-4'-diaminodifenilsulfona. Las dos sulfonas, el derivado del ácido tridiamidofosfórico y el promizol, obtuvieron un retardo del proceso tuberculoso comparado con el debido a la diaminodifenilsulfona, pero el promizol es el más tóxico de los dos. De los tres sulfonamidos la sulfabenamida resultó demasiado tóxica, la irgamida suministró poca protección y el irgafén produjo efecto ligeramente favorable.

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ANATOMICAL STUDIES ON HUMAN TUBERCULOSIS¹

XIX. Protracted Primary Tuberculosis in the Adult, with Some Observations on "Lymphoglandular-Endogenous Reinfection (Ghon)"

KORNEL TERPLAN

In this paper we wish to present the anatomical findings in 6 cases, which obviously differ from those of comparatively recent primary tuberculosis in the adult discussed in the preceding paper (1). In 5 of them the primary focus was in a healed state. The tuberculous process in the lymph nodes regional to the focus, however, was of less uniform structure. While some lymph nodes closest to the primary lesion were also in an obsolete state, there were other lymph nodes in orthograde direction with anatomically not completely healed tubercles and, in addition, with more recent-appearing tuberculous changes. No postprimary tuberculous lesions were present in the lungs which could have been interpreted as the result of exogenous superinfection or reinfection, causing the more recent tuberculous changes in the lymph nodes. It seemed as if the tuberculous process also found in such organs as the adrenals, or recent scattered hematogenous tubercles in the lungs, were pathogenetically linked to persistent active tuberculous changes in the lymph nodes within the confines of or closely contiguous to the original primary complex. As exogenous reinfection lesions were absent, we felt that pathogenetically these cases should be considered as primary infections, in spite of the fact that signs of activity had apparently disappeared not only in the primary focus but also in the nearby parenchyma and, to a large part, in the regional lymph nodes forming the complex. At least 4, but possibly 5, of our cases represent a combination of healed, chronic and active tuberculous lesions in bronchomediastinal lymph nodes regional to an obsolete primary focus, usually referred to as endogenous-lymphoglandular reinfection or exacerbation. It could also be defined as protracted lymphoglandular progression. Only in one case included in this series (no. 4145) is this picture absent. Although the primary lesion or lesions were obscured, we have included this case in our series because the final anatomical picture suggested an older process in two subpleural lymph nodules. In this case it was, apparently, not lymphogenous exacerbation but progressive caseation of the spine, caused by the preceding primary infection, which had led to overwhelming miliary tuberculosis. The bronchomediastinal lymph nodes, however, showed most massive recent involvement, demonstrating once more that actively progressing pulmonary lesions, regardless of their pathogenesis—primary or post-primary—are apt to lead to considerable lymphogenous spread which in turn might contiguously affect the bronchial tree.

Before presenting the anatomical findings in some of our cases with changes usually interpreted as lymphogenous endogenous exacerbation or, preferably, as

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protracted lymphoglandular progression, some reference should be made to the literature on this "endogenous-lymphogenous reinfection." The term "endogenous reinfection" was used first by Orth. According to Orth, it meant the manifestation of a new infection in a harbinger of tuberculous lesions by the same tubercle bacilli which had infected the body originally. It is, therefore, in terms usually applied in general pathology, a recurrence. This term "endogenous reinfection" was amplified by Ghon (2) with the adjective "lymphoglandular" referring specifically to the type which is caused by a local reactivation and extension within lymph nodes, the site of older tuberculous lesions, while the primary focus appears completely healed. It will remain to the credit of Ghon and his pupils, Pototschnig, Kudlich and Schmiedl, that these combinations of obsolete older and more recent lesions in the bronchomediastinal lymph nodes became known to the student of tuberculosis. It is immaterial in our present discussion whether this reactivation of the tuberculous process followed a state of apparently long latency, as Ghon thought in his first publication on endogenous reinfection, or whether an exacerbation of the bronchomediastinal lymph node tuberculosis recurred in several phases. Ghon (3), in one of his subsequent publications on reinfection, leaned toward this latter view. In this paper in which 6 cases were analyzed, ranging from thirty-one to sixty-eight years, an exogenous source for the active lesions in the bronchomediastinal lymph nodes could be excluded with certainty by Ghon. Later, in collaboration with Kudlich and Schmiedl (4), the angulus lymph nodes from 100 cases of all age groups were systematically examined in serial sections. This material included many children and young adults. In a great majority (84 per cent) of all cases studied, tuberculous lesions of various ages were found in the angulus lymph nodes. Ghon believed that in these cases a new endogenous infection of the lungs could be brought about by the propagation of the tuberculous process through the systemic veins. He expressed the view that such a gradual lympho-hematogenous propagation might stay restricted to the lungs.

Regardless of whether or not this conception of Ghon, in its pathogenetic relation to pulmonary tuberculosis, will be corroborated by further studies, it will remain his great merit that he first called attention to the frequency of chronic and active tuberculous lesions in bronchomediastinal lymph nodes regional to obsolete primary foci, thus pointing to a possible source for further hematogenous spread from reactivated or persistent tuberculous lesions in the lymph nodes of the old primary complex. Murano (11) claimed that intermittent bacilleemia with a lymphoglandular focus as its source, usually limited to the lesser circulation, is the important factor in the pathogenesis of chronic miliary tuberculosis in the lungs in general. Wallgren (12), however, stated that lymphoglandular exacerbation in the primary complex may occur as well from endogenous as, possibly, also from exogenous sources.

The findings of Ghon and his pupils on "endogenous reinfection" in the bronchomediastinal lymph nodes were confirmed by others. Anders (5) found postmortem in 35 per cent of 1,500 cases over forty-five years of age recent tuberculous lesions in the bronchomediastinal lymph nodes. He felt that

isolated organ tuberculosis and miliary tuberculosis are late manifestations of the primary infection. On the other hand, he advocated the hypothesis that true exogenous reinfection may exert a stimulating effect upon quiescent tuberculosis in the lymph nodes of the old primary complex, leading to endogenous exacerbation. (On the basis of our own studies on reinfection, we cannot agree with this latter view of Anders.) Schuermann (6), in his systematic studies on tuberculosis in adults, found 46 cases between forty-one and eighty-five years of age with lymphoglandular exacerbation, meaning stony tuberculous lesions combined with tuberculous hyperplasia. This number represents 5.38 per cent of all his cases with a typical primary complex. He cautioned, however, against interpreting such lesions as a proved source for further hematogenous spread. As against 20 cases without hematogenous metastases, Schuermann found only 2 in which hematogenous lesions had apparently followed lymphoglandular exacerbation. The average age at which Schuermann noticed endogenous exacerbation in lymph nodes was fifty-three.

Kalbfleisch (7), in a study of tuberculosis in old age, found changes of endogenous exacerbation in the bronchomediastinal lymph nodes in 31.5 per cent of his material. In not a single case, however, had this exacerbation caused hematogenous metastases. Kalbfleisch concluded from his own study that endogenous lymphoglandular exacerbation is harmless in the older age groups. More recently, Staemmler and Otto (8) made the pathogenetic significance of endogenous reactivation of the primary complex the subject of a study in 97 cases. There was neither gross nor microscopic evidence of active pulmonary tuberculosis in this material. In not a single instance was there any finding pointing to reactivation of the primary focus proper. Active tuberculous changes in hilar lymph nodes were observed in 19 per cent. One-third of these 19 per cent were from age groups above fifty. According to Staemmler and Otto the active tuberculous changes in lymph nodes have a tendency to heal. Although it is admitted that they remain a potent source for hematogenous dissemination, such a spread had not occurred in their 97 cases.

That active tuberculous lesions in the bronchomediastinal lymph nodes regional to a primary focus—and this applies also to mesenteric and celiac lymph nodes regional to primary intestinal tuberculosis—can furnish the direct source for hematogenous tuberculosis, no one will deny. Such lesions, either slowly progressing or possibly reactivated under unfavorable dispositional changes—as seen following nontuberculous pulmonary infections like measles or grippous inflammations—appear of great importance in the pathogenesis of miliary dissemination in various organs, or sometimes of tuberculous meningitis alone. Aschoff (9), in discussing Ghon's paper on tuberculous reinfection in man, confirmed the findings of Ghon, especially in regard to endogenous-lymphogenous reinfection in the puberty age. At the same time, however, he called attention to the fact that in cases with obviously hematogenous tuberculosis of various organs, especially of adrenals, kidneys, testicles or the skeleton, the lungs usually are not involved. In our paper on tuberculosis in children (10), we have briefly mentioned 3 instances in which endogenous-lymphogenous exacer-

bation seemed to culminate in tuberculous meningitis without leading to generalized miliary tuberculosis.

The relationship of endogenous-lymphogenous progression or exacerbation to hematogenous tuberculosis in general is well established by many postmortem observations, especially in childhood. The paramount question, however, is whether or not this endogenous-lymphogenous "reinfection" is of pathogenetic importance for the development of pulmonary tuberculosis or phthisis, of the so-called "reinfection type" in the adult in particular. Only with this specific point in mind I have restudied the material on endogenous reinfection, reported by Ghon and his pupils. In the first paper (Ghon and Pototschnig (2)) entitled *Über den primären tuberkulösen Lungenherd beim Erwachsenen nach initialer Kindheitsinfektion und nach initialer Spätinfektion und seine Beziehungen zur endogenen Reinfektion*, there is no instance included in which the tuberculous process in the mediastinal lymph nodes was associated with recent progressive tuberculosis in the lungs. One case (no. 5) showed a few minute hematogenous tubercles in both upper lobes, spleen, liver and kidneys. In this case as well as in the protocol of several others, it is expressly stated that the apices were free. The tuberculous process which was found in a reactivated state in the lymph nodes—after an apparently long latency—had, apart from a few minute hematogenous tubercles, remained restricted to the bronchomediastinal nodes. In a second paper (Ghon and Kudlich (3)) entitled *Zur Reinfektion bei der menschlichen Tuberkulose*, 6 cases were reported with lymphoglandular-endogenous reinfection in bronchomediastinal lymph nodes regional to an obsolete primary focus. Their ages were twenty-six, thirty-one, fifty-two, sixty, sixty-one and sixty-eight years. Only in one of them was there a single interstitial tubercle of microscopic size found in each apex, consisting of epithelioid and giant cells with round cells, but without caseation. In the lymph nodes of all these 6 cases there were calcified lesions, numerous hyaline tubercles and, in close relation to these, recent tubercles. An exogenous source for these active tuberculous lymph node lesions could be definitely ruled out by Ghon. The lungs were carefully examined and, except for the recent microscopic tubercle in each apex of one case, there were no tuberculous lesions in the lungs apart from the old focus. It is in this paper in which Ghon expressed the opinion that the microscopic tubercles in the apex of each upper lobe might have initiated a further spread of tuberculosis in the lungs.

The entire material presented in both papers referred to proves the presence of old and more recent tuberculous lesions within the lymph nodes. It is remarkable that in some of these cases in which most of the bronchomediastinal lymph nodes showed even grossly tuberculous hyperplasia there was no evidence of hematogenous dissemination.

In another paper (Ghon, Kudlich and Schmiedl (4)) entitled *Die Veränderungen der Lymphknoten in den Venenwinkeln bei Tuberkulose und ihre Bedeutung: Eine Studie zur Frage der Reinfektion*, the axillary lymph nodes in 100 cases were studied after serial sectioning. Many of these cases were children and young adults, representing the age groups in which pulmonary tuberculosis is most

commonly observed. There were 45 cases of childhood and prepuberty age and 37 cases from fifteen to forty years of age; the remaining 18 cases were between forty-one and seventy years.

In no instance had definite proof been presented that the pulmonary tuberculosis was caused by lympho-hematogenous "reinfection." In many cases the pathogenesis of the pulmonary lesions seemed clearly linked with exogenous superinfection or reinfection. In 4 out of 10 cases specifically tabulated, the possibility of endogenous reinfection is discussed, although it is frankly stated that exogenous superinfection or reinfection could just as well be responsible for the tuberculous pulmonary lesions. In discussing one of these 4 cases (no. 68) Ghon *et al.* admit that the tuberculosis in the lymph nodes of the left venous angle might be secondary to an exogenous reinfection. There are also cases included in this study in which, in the presence of a typical calcified complex with chronic fibrocased pulmonary tuberculosis and tuberculous lesions in the regional lymph nodes, the angulus lymph nodes were definitely free of tuberculosis.

It appears, then, since in no case out of the material reported by Ghon and his pupils, a *progressive "endogenous reinfection tuberculosis of the lungs"* has been proved beyond any doubt, that the practical importance of endogenous-lymphogenous exacerbation in its pathogenetic relation to pulmonary tuberculosis is of no great significance. Ghon, Kudlich and Schmiedl consider as the most important result of their extensive study that in the great majority of cases of pulmonary tuberculosis of various age groups, including childhood, puberty and adult life, tuberculous lesions of various structural age have been found in the lymph nodes of the venous angles. Although Ghon seemed to believe that in these cases a new progressive infection of the lungs can be brought about from the propagation of the tuberculous process through the jugular veins, the material presented in his papers on endogenous reinfection has not furnished an unequivocal proof for this view. The value of these studies, however, remains great regardless of their interpretation. No systematic morphological studies of the angulus lymph nodes had been undertaken by anyone before, and their common involvement in various forms of pulmonary tuberculosis has become, on the basis of Ghon's studies, an established fact. In the light of morphological research in the last fifteen years, continued on the solid foundation laid by the careful, methodical work of Ghon, it might be added that his studies on lymphoglandular-endogenous reinfection are perhaps of greater value in pointing—at least in the large majority of his observations—to the absence of progressive pulmonary tuberculosis in relation to the primary complex rather than in proving such a pathogenetic correlation.

Our own anatomical observations are listed in table 1. A few of these will be discussed in some detail.

Case 1: (B. G. H. 5283) seventeen year old colored female. Cause of death: uremia from subacute glomerulonephritis.

The following tuberculous changes were incidentally found postmortem: There was a firmly hyalinized tubercle, about pea-sized, in the lower half of the left lower lobe, sur-

TABLE 1
Anatomical findings in 6 cases of protracted primary tuberculosis in adults including lymphoglandular—endogenous reinfection

CASE NUMBER	AGE, RACE, SEX	PRIMARY COMPLEX	EXTENSION IN THE LUNGS	HEMATOGENOUS SPREAD	SPECIAL REMARKS
5283	17, Colored F	Primary focus, pea-sized, firmly hyalinized; lower part left lower, with several bacillary scars. Ro-cent cavitation of one regional upper tracheobronchial lymph node, combined with hyaline tubercles	A few small recent as-piration tubercles in right middle, left up-per and left lower	A few lentil-sized tubercles in the spleen	Lymphoglandular exacerba-tion with direct rupture into the major bronchus (inci-dental finding). Cause of death: uræmia from chronic glomerulonephritis
4878	33, Colored F	Firm stony complex with two minute foci; lower lateral part right upper, with perifocal fibrosis. Firm calcification in regional bronchopulmo-nary and part of one upper tracheobronchial lymph node with massive exacerbaton in re-mainder of this node, anterior mediastinal and left angulus lymph nodes	No intrabronchial spread	Massive military spread in spleen, liver, lep-to-meninges with cortical tubercles. A few scat-tered pinhead to pea-sized tubercles in both lungs	Lym-phogonous spread in peri-pancreatic and peripor-tal lymph nodes. Gastro-in-testinal tract, mesenteric nodes negative
2951	63, White M	Few fibrocalcified tubercles; subapical left upper, with perifocal scarring. Small calcified tubercle in one regional upper tracheobronchial lymph node and massive exacerbaton with large cavities in left paratracheal and left angulus lymph nodes	No intrabronchial spread	Massive military tuberculosis in liver, spleen and kidneys. Scattered hematogenous tubercles in both lungs	Considerable lymphogonous spread in peripor-tal, peri-pancreatic and periaortic lymph nodes
3526	35, White F	Several calcified complexes: three calcified foci (about 2 mm.); base left lower, hilar level, left upper. Firm calcification of left bronchopul-monary, lower and upper tracheobronchial lymph nodes, crossing over to some right bron-chopulmonary and right paratracheal nodes. More chalky and fibrocaseous lesions in anterior mediastinal nodes	No intrabronchial ex-tension	Complete caseous destruction of adrenal glands. Rare small fibrocaseous tubercles in liver, kid-neys and spleen	Lym-phogonous progression to peripancratic and peripor-tal lymph nodes. Cause of death: Addison's disease
5160	76, White M	Fibrous chalky-calcified complex, primary focus left lower. Chalky-calcified changes restricted to left bronchopulmonary and lower tracheobronchial lymph nodes. Massive exacerbaton with recent caseation in lower and upper tracheobronchial lymph nodes extending into the ve-nous angle nodes	Single, old localized fibrous-chalky focal extension in left lower. No recent intrabronchial spread	Massive caseated tuberculous pleuritis; right lung, with marked lymphogenous progression from this side. Generalized military spread in lungs, spleen, kidneys, adrenals, peritoneum and meninges	No apical or subapical lesions except for recent military tu-bercles. Tuberculous hyper-plasia of peripancratic and periaortic lymph nodes
4145	40, Colored F	Primary foci obscured; two chalky subpleural lymph nodules; interlobar surface, hilar level left upper and left lower. Small hyaline con-glomerate tubercles in a regional left broncho-pulmonary lymph node	No intrabronchial spread	Massive caseation of seventh and eighth dorsal vertebra. Overwhelming military tuberculosis in all lobes. Massive tuberculous hyperplasia with moderate caseation of all bronchomediastinal lymph nodes. Dense military tuberculo-sis in liver, spleen, kidneys. Military tubercles in thyroid, bladder, myocardium	Intestinal tract free. Head not dissected; clinically typical meningeal symptoms

rounded by irregular hyalinized scars in the lung tissue. There was no calcification in this lesion. The X-ray picture showed a few minute chalky deposits in a tracheobronchial lymph node filling out the upper tracheobronchial angle. This node had the size of a large date. In its periphery there were a few fibrous-hyalinized confluent tubercles. The centre, however, contained soft, pus-like caseated material. The attached bronchial wall was distinctly bulging toward the lumen. Grossly, a perforation could not be noticed. There was, however, the typical finding of early aspiration tuberculosis with a few recent, nearly cherry-sized bronchial tubercles in the right middle lobe and a few smaller acinous tubercles in the lower part of the left upper lobe and in its apex.

The histological analysis of the fibrous focus, its surrounding structures, of the bronchomediastinal lymph nodes and the tuberculous lesions from the left and right lung gave a clear picture (plate 1): The fibrous lesion in the left lower lobe (B) was a scar, irregularly defined, with considerable retraction of the pleura and complete fibrous organization of a small branch of a pulmonary artery attached to the scar. Histological serial sections through the date-sized lymph node closely attached to the obtuse upper tracheobronchial angle revealed distinct perforation of the bronchial wall (A). The cortex of this node, its capsule and the perihilar tissue were in part hyalinized. The bulk of the tuberculous lymph node tissue, however, showed recent caseation and liquefaction necrosis. The massive perforation as seen in photograph "A" had been missed at gross inspection.

The few tubercles found in the left upper and in the right middle lobe showed the typical histological picture of tuberculous bronchitis and peribronchitic pneumonia with considerable recent caseation, most marked in the right middle lobe. The perforation through the bronchus was present only in a few sections of a series cut through the date-sized lymph node and the attached bronchial wall.

Epicrisis: In our anatomical material on tuberculous findings, this is a rather unusual experience. Fibrous obliteration of a primary pulmonary focus without traces of calcification is still the exception. Histological analysis of the area surrounding the scar showed a few nodular hyalinized lesions in which most of the blood vessels appeared well preserved in the elastic tissue stain. Scattered hyalinization surrounding a few emphysematous areas was present in a close radius around the hyaline focus. The patient was observed in the hospital for only seven days previous to death. While she showed all the symptoms of progressive renal failure, with uremia, there was coarse wheezing all over the chest at inspiration and expiration, and increased fremitus about the anterior right chest. The roentgen photograph showed partial obliteration of the costo-diaphragmatic angle on the left side and the hilar shadow was distinctly enlarged. One-half year previous to death the X-ray picture had been negative. Relative to tuberculosis, it was learned from the chart that the patient had been seen occasionally—during the last six months—in the eye clinic of the outpatient department, where she was treated for phlyctenular kerato-conjunctivitis of possibly tuberculous nature. Following a tuberculin test (Mantoux) five months previous to death, which was strongly positive, the phlyctenular kerato-conjunctivitis appeared much more marked (reactivated) than when first observed, pointing to considerable tuberculin hypersensitivity. Hematogenous spread in this case was restricted to a rare lentil-sized, completely caseated tubercle in the spleen.

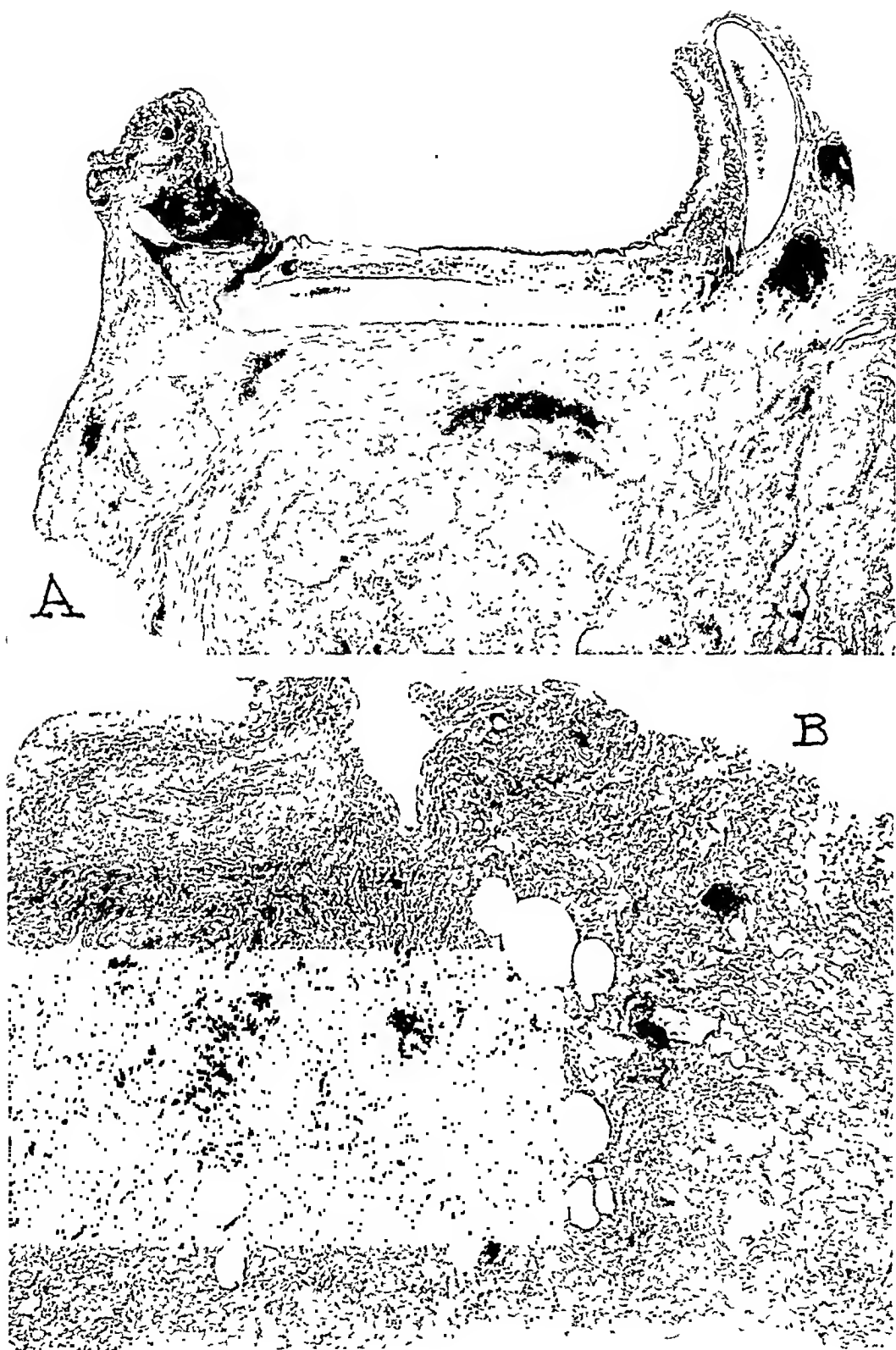


PLATE I

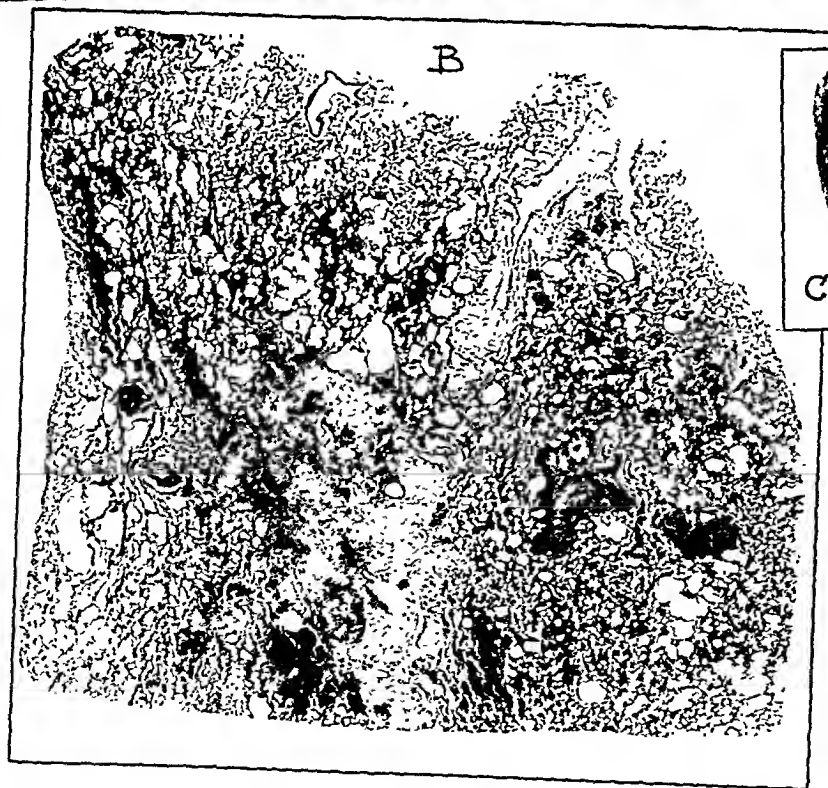
We feel, then, that this case represents a clear example of lymphoglandular exacerbation in the presence of an entirely healed primary lesion in the pulmonary parenchyma. The unusual complication is that this exacerbation had involved the lymph node capsule, leading to perforation of the contiguous bronchial tube, with recent scattered intrabronchial spread. Gross and histological analysis of the few tubercles found in the left upper and right middle lobe pointed to a bronchial rather than to a hematogenous source. Among the factors responsible for this acute exacerbation in the tracheobronchial lymph nodes causing diffuse liquefaction necrosis, a focal hypersensitivity reaction to the administration of tuberculin should be considered. Not only did an X-ray photograph taken at a time shortly preceding the tuberculin testing give an entirely normal picture of the lungs and the mediastinum, but also the considerable focal reactivation of the phlyctenular kerato-conjunctivitis, observed together with the strongly positive Mantoux test, would favor such an assumption.²

Case 2: (B. G. H. 4878) Thirty-three year old colored female. Cause of death: miliary tuberculosis, tuberculous meningitis. Only a condensed anatomical-histological report will be given.

There were two minute, firmly calcified, in part slightly ossified tubercles in the lower lateral part of the right upper lobe, with the nearby parenchyma distinctly fibrotic, especially around several bronchi. There were a few firmly encased stones in the regional bronchopulmonary and in one upper tracheobronchial lymph node, and a small subpleural calcified nodule at the level of the parenchymatous foci. In one of the upper tracheobronchial lymph nodes containing small calcified splinters there was, in addition, irregular hyalinization along with diffuse tuberculous hyperplasia, suggesting grossly so-called "endogenous exacerbation." In other nodes of this group and in the anterior mediastinal lymph nodes and the nodes of the left venous angle there was diffuse hyalinization with confluent caseated conglomerate tubercles. Scattered over both lungs there were pinhead to lentil-sized soft tubercles in small numbers. The apices were not involved. The histological picture of the pulmonary tubercles was uniformly the same, showing tuberculous lesions of the miliary pattern, hardly involving more than an alveolus and the surrounding stroma. Some of them, however, were larger, occasionally including a bronchiolus. In the smaller nodules there was central caseation. In contrast to these relatively few scattered tubercles in the lungs, there was massive hematogenous involvement of the spleen, with a tuberculous splenic tumor (weight 980 g.), and marked hematogenous tuberculosis of the liver with nodular bile duct tubercles. Peripancreatic and periportal lymph nodes showed extensive tuberculous hyperplasia. There were scattered tubercles in both adrenals and in the kidney, and massive tuberculous meningitis with a few large meningeal and small cortical tuberculomata.

It was our impression, on gross examination, that we were dealing with protracted hematogenous tuberculosis originating in the lymphoglandular component of the primary complex. The primary parenchymatous lesions were entirely obsolete, while some of the regional lymph nodes showed a combination of older and more recent structural changes described as "lymphoglandular exacerbation." (All bronchomediastinal lymph

² It should be mentioned that the association of uremia with changes of lymphogenous endogenous exacerbation has been incidentally observed in 5 out of 29 cases in Schuermann's material (6).



nodes, the obsolete tuberculous lesions in the right upper lobe, the recent tubercles from left and right lung and the lymph nodes in the venous angles were examined completely.)

Plate 2 (B) shows the hyalinized and calcified remnants of a locally spreading primary lesion; also, to the right, one recent tubercle, apparently blood-borne. "C" shows a calcified tubercle in a right bronchopulmonary lymph node, along with a minute hyalinized tubercle. Picture "A" shows a right upper tracheobronchial lymph node with some fibrous-chalky changes; to the right, part of the chalky material (most of it had fallen out in the process of cutting) with contiguous hyalinization and fibrosis; in the remainder, recent conglomerated epithelioid cell tubercles. In other parts of this node there were a small calcified splinter and smaller fibrous tubercles.

In the scattered, recent tubercles within the pulmonary parenchyma the tendency to fibrous organization was very marked. Only in a few of them was there still central caseation. The pulmonary tissue surrounding the endobronchial tubercles did not show any further spread. The hematogenous spread in the lung was minimal in comparison with the massive tuberculosis of spleen, liver and brain. On the X-ray film of the lungs, taken postmortem, the former was not noticeable at all. There were no signs of endobronchial progression from these small, obviously hematogenous tubercles. The lymph nodes draining the left upper lobe were entirely negative, although there were scattered hematogenous tubercles in the lobes of the left lung.

The interpretation of the diffuse caseated tuberculous lesions in the lymph nodes of the left venous angle is complicated by the considerable lymphogenous tuberculosis of the peripancreatic and periportal lymph nodes. There was gross evidence that the tuberculosis of these nodes had extended to several retro-mediastinal lymph nodes, including the entirely caseated node in the left pulmonary ligament, while the left lower tracheobronchial lymph nodes contained only a few epithelioid cell tubercles. Apart, then, from the typical lymphoglandular exacerbation in the left upper tracheobronchial lymph nodes there was an additional source in the retromediastinal lymph node chain for the recent tuberculous lesions in the lymph node of the left venous angle. The few epithelioid cell tubercles in the left lower tracheobronchial lymph nodes were secondary either to the recent tuberculous lesions in the lymph node of the left pulmonary ligament or to the active tubercles in the left upper tracheobronchial lymph nodes, the site of the "exacerbation." The clinical history further tends to complicate any clear pathogenetic analysis in so far as two years previous to death the cervical lymph nodes were enlarged, although at postmortem no gross tuberculosis was seen in these nodes (they were not examined histologically). The gastro-intestinal tract and all mesenteric lymph nodes were free of tuberculosis. In another respect, the gross and histological findings are noteworthy in this case. The remnants of the primary infection point to a distinct focal extension close to the two obsolete calcified primary tubercles.

The culture taken from the caseated tubercles in the spleen yielded an abundant growth of tubercle bacilli of the human strain.

The patient was admitted twenty-four days previous to death. Chest X-ray was negative. The main symptoms were of neurologic nature, pointing to tuberculous meningitis.

Case 3: Another example of clearly endogenous lymphoglandular exacerbation is presented by the following case (B. G. H. 2951), a sixty-three year old white male. Cause of death: miliary tuberculosis.

The pertinent anatomical findings follow: There were two small stony tubercles included in hyaline scar tissue in the upper third of the left upper lobe. In one left upper tracheobronchial lymph node there was localized calcification. The contiguous left paratracheal lymph node and the lymph nodes of the left venous angle showed older firm caseation combined with cavity formation. One of the lymph nodes in the left venous angle was almost entirely replaced by a cavity nearly 1 cm. in diameter. The right lung was free. The gross findings were interpreted as endogenous exacerbation in the lymph nodes regional to an obviously healed primary fibrous-calcified tuberculous infiltration in the upper third of the left upper lobe.

The histological examination of the fibrotic lesions in the left upper lobe revealed small calcified splinters within hyaline scar tissue. There was no active tuberculosis in and around these scars. There were, however, a few small nontuberculous bronchiectatic cavities included in the scar tissue. The hematogenous tuberculosis was very marked in spleen, liver and kidneys, while in both lungs there were only a few scattered miliary tubercles which, in the histological picture, showed a typical structure of recent miliary caseated tubercles involving a few alveoli. The histological picture of the left angulus lymph nodes was that of diffuse caseation with central disintegration, with hyaline changes in part of the capsule.

There was no history of a tuberculous infection at any time. The patient, a sixty-three year old white male, suffered from heart trouble and chronic arthritis for one year previous to admission. He was seen in the hospital only for a few days before he died. Some physical findings were suggestive of miliary tuberculosis.

Case 4: (B. G. H. 3526) A thirty-five year old white male. The gross and histological findings and the X-ray photograph of the lung appeared rather clear in designating this case as one of lymphogenous exacerbation or protracted lymphogenous progression. There were three minute calcified tubercles, one in the lower lateral area of the left lower lobe and two similar lesions in the midportion of the left upper lobe. All regional lymph nodes, including the left lower and upper tracheobronchial and the anterior mediastinal groups, and, in addition, the right paratracheal and a few right bronchopulmonary nodes in the hilum showed very firm calcified and calcified-chalky changes. In the anterior mediastinal lymph nodes, however, the tuberculous process was in part still in a fibrocaseous state. Both adrenal glands were completely destroyed by caseation. There were a few rare fibrocaseous tubercles in liver, kidneys and spleen. Periportal and peripancreatic lymph nodes showed considerable chalky and fibrocaseous tuberculosis.

This case was interpreted as a primary pulmonary tuberculosis with a few entirely calcified primary tubercles in the left lung and with chalky, fibrocaseous lymphoglandular progression or exacerbation in the regional anterior mediastinal group, leading to massive tuberculosis of the adrenal glands and but minimal hematogenous tubercles in liver, spleen and kidneys. There was neither intrabronchial progression nor were there hematogenous tubercles in the lungs. The intestinal tract was free.

Only the following clinical data were available: The patient was well until twelve days previous to admission. His skin had been bronzed for some time. He was hospitalized with the fully developed clinical picture of Addison's disease and died on the following day.

In our next case the anatomical findings are too extensive and complicated to permit an unequivocal analysis as to the sources for lymphoglandular exacerbation. We have included this case for the following reason: It represents a relatively late primary infection combined with obviously protracted hematogenous tuberculosis of the lung.

Case 5: (B. G. H. 5450) Seventy-five year old white male. Cause of death: miliary tuberculosis. (Plates 3 and 4)

There is a peculiarly shaped, apparently fragmented, chalky-calcified primary focus about the size of a hazelnut in the basal portion of the left lower lobe near its posterior surface, with distinct chalky-calcified deposits in the lymph nodes of the left pulmonary ligament, of the left bronchopulmonary group at the hilum, and in the lower tracheobronchial nodes. A well encapsulated focus of soft consistency, measuring 1×0.6 cm., was found 1 cm. medial to the primary lesion. It contained almost liquid, creamy, caseous material. There were no adhesions around the left lung. In the right pleural cavity there was about 500 cc. of slightly hemorrhagic exudate. The middle lobe was firmly adherent to the pericardial sac and to the upper and lower lobes, the costal surfaces of which were for the most part adherent to the parietal pleura. Distinct tuberculous granulations were grossly noticed on the base of the right lower lobe and on the parietal pleura where the pleural space was not obliterated. All lymph nodes in the right pulmonary ligament showed grossly marked tuberculous hyperplasia. These same changes were seen in the lower tracheobronchial lymph nodes, which were about plum-sized, with the small chalky-calcified lesions, mentioned above, clearly noticeable on the cut surface. Massive tuberculous hyperplasia was present also in both upper tracheobronchial and paratracheal and in the anterior mediastinal lymph nodes. The lymph nodes in each venous angle showed marked hyperplasia with fairly diffuse caseation.

The entire right lung was cut in numerous gross serial sections. No subpleural focal lesion was found anywhere, but only the typical picture of miliary tuberculosis. The distribution of miliary tubercles was much more dense in both lobes of the left lung than in the right.

There was massive hematogenous tuberculosis of the spleen, with considerable enlargement (weight, 700 g.), scattered miliary and conglomerate tubercles in kidneys and adrenals and extensive tuberculous peritonitis with very dense dissemination of tubercles all over the visceral and parietal peritoneum. Except for one single lentil-sized ulcer in the lowest part of the ileum, the gastro-intestinal tract was free. In the mesenteric lymph nodes there were a few miliary tubercles. Scattered pinhead-sized meningeal tubercles were seen on the convexity of the brain, but no parenchymatous tubercles in the brain substance.

Our impression on gross examination, to some extent influenced by the X-ray photograph of the postmortem specimen, was that the soft focus found close to an apparently old primary lesion was a relatively recent focus of true reinfection, from which considerable lymphogenous extension had led to miliary tuberculosis and tuberculous pleuritis. It was evident from both the gross inspection and the X-ray photograph that there were no older apical or subapical lesions. The calcified deposits in the primary focus and in some



A



B

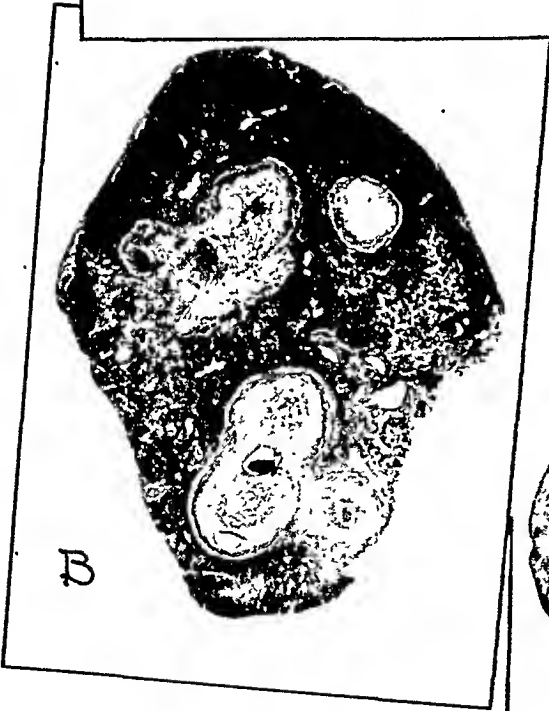
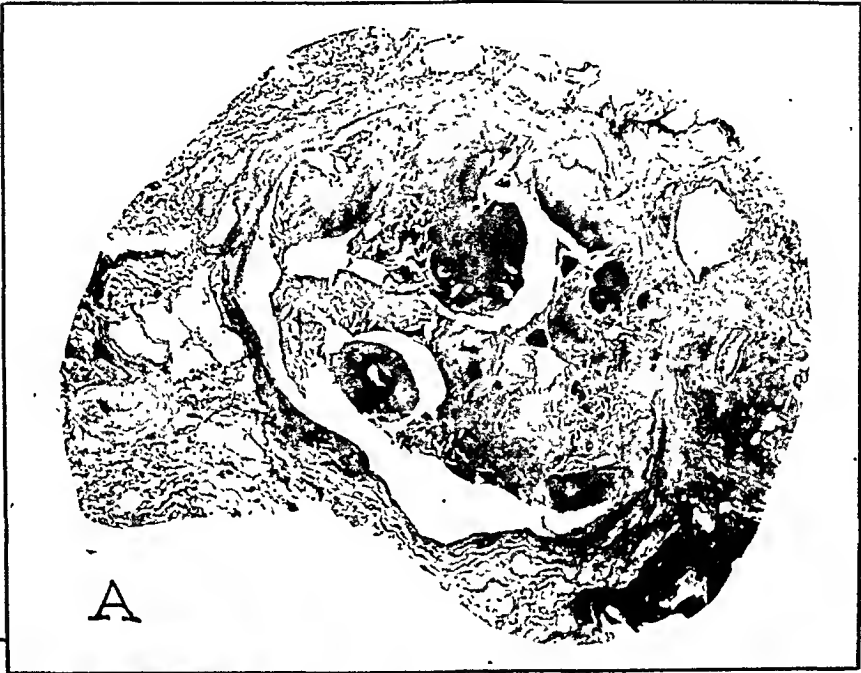


PLATE 4

of the regional lymph nodes were the only changes pointing to an old primary complex. In fact, we leaned somewhat to interpret the fragmented appearance of closely agglomerated calcified tubercles as a very old primary lesion with considerable resorption of the calcified matter by bone marrow.

A complete histological examination of the primary lesion and the nearby "reinfection" focus, along with several sections from both lungs and all groups of the bronchome-diastinal chain yielded some surprises. The primary focus, part of which is shown on plate 3 (B), differed considerably from the usual picture of a primary lesion. It consists of several chalky-hyalinized and only slightly calcified tubercles within small bronchi, extending to the peribronchial tissue. These are in more or less close agglomeration but not completely fused together. There is some fibrosis and both atelectatic tissue and air-containing parenchyma between the individual hyaline and chalky tubercles. Within the air-containing lung tissue, separating the chalky tubercles in the periphery from the larger central focus, there are a few recent miliary tubercles (part of the generalized recent miliary seeding). Only serial sectioning through the entire area of the primary focus revealed that it was composed of several hyalinized-chalky tubercles. The largest of these had formed within and around a bronchus and had caused considerable fibrosis within the interlobular septal tissue along the course of an arterial branch. Between this area and the parietal pleura there was atelectasis. A closer examination of the X-ray photograph demonstrating the primary lesion shows that it consists of multiple tubercles forming a rather loose cluster. (Plate 3, A)

In all lymph nodes of the left pulmonary ligament, the left bronchopulmonary and the left lower tracheobronchial group, in which calcified or chalky foci were disclosed by the X-ray photograph and by gross dissection, it was found that most of these were chalky-fibrous conglomerate tubercles but that a few of them contained small central stones. The histological structure of these older tubercles in the lymph nodes is very similar to the larger tubercles composing the primary focus. Plate 4 B shows a low power view of one of these lymph nodes from the bronchopulmonary group at the hilum of the left lower lobe. In addition, most of these lymph nodes show extensive recent tuberculosis with confluent epithelioid giant cell tubercles and slight caseation. The distinction between old and new tubercles is very clear.

A section through the soft creamy focus (plate 4, A), which was not noticeable on the X-ray film, shows a large tuberculous lesion within a bronchus. Most of the bronchial wall is hyalinized, but in a small portion of the circumference ciliating epithelium is still preserved. The bronchial lumen is filled with caseated and slightly chalky matter containing lipid debris with cholesterol crystals.

Although it was felt originally that this lesion was a reinfection focus, the histological comparison between the primary lesion and this soft focus makes it more probable that we are dealing with either a restricted superinfection or with focal extension from one of the chalky-fibrous foci forming the primary lesion. The pulmonary parenchyma surrounding this soft secondary focus shows some hyalinization near its capsule.

Sections from various parts of the left lung show the typical picture of miliary tuberculosis with the tubercles very closely arranged, some of them involving small bronchioli. There is distinct alveolar emphysema between some of the tubercles. The sections taken through the left upper tracheobronchial, anterior mediastinal, paratracheal and angulus lymph nodes show unusually massive, diffuse caseation and moderate hyalinization, especially near the capsule. These changes are of fairly uniform character in all these lymph node groups. In none of these are there old chalky-fibrous tubercles, such as were found in the lymph nodes at the hilum of the left lung and in the lower tracheobronchial group. Plate 4, C shows a section through one of the left angulus lymph nodes.

Sections taken from various parts of the right lung, including a large number through the tuberculous pleura and the contiguous pulmonary tissue, show the typical picture of chronic caseated tuberculous pleuritis with large conglomerate tubercles and very active tuberculous granulations. The dissemination of miliary tubercles in the pulmonary tissue is, in general, much less marked than in the left lung. The miliary tubercles appear more dense and conglomerated only in some sections, encroaching upon smaller bronchi, with recent tubercles in their mucosa. Much of the fibrinous tuberculous exudate on the surface is in process of organization.

Sections taken through the bronchomediastinal lymph nodes on the right side, including the right pulmonary ligament, lower and upper tracheobronchial, paratracheal and anterior mediastinal group, show extensive caseation, with epithelioid cell tubercles and slight hyalinization, again closer to the cortex. There are no chalky or firm fibrous tubercles.

Epicrisis: The histological analysis showed a much more complicated picture than was expected from the gross and X-ray findings. The primary focus consisted of multiple small firmly hyalinized-chalky bronchial and peribronchial tubercles and a few satellite tubercles with similar regressive changes, all in an area of about 1.5 cm. in diameter, pointing to a localized focal intrabronchial extension at the time of the first infection. All the regional lymph nodes at the hilum of the left lung showed about the same degree of regressive changes with comparatively little calcification. In spite of formation of a few small stones within these chalky-caseated tubercles, the entire picture was decidedly different from an old obsolete complex. It is suggestive of a relatively late primary infection. The generalized miliary tuberculosis is apparently in connection with the massive caseation found in both upper tracheobronchial, paratracheal and mediastinal groups, extending on the left side clearly into the lymph nodes of the venous angle. Whether or not it was preceded by the tuberculous pleuritis around the right lung cannot be decided with certainty. The tuberculous pleuritis as well as lymphogenous exacerbation and progression in the various groups forming the primary complex could have participated in this final picture of massive lymphogenous spread with miliary tuberculosis. It seems as if the extensive tuberculous pleuritis within the right pleural cavity had preceded the massive hematogenous seeding in both lungs, as there was no tuberculous pleural involvement around the left lung.

The patient's chart gave the following information: He had suffered from anemia for the last year. Twenty days previous to death, when he was admitted to the hospital, he complained of dyspnea, fatigue and generalized weakness. Physical and roentgenological examination revealed fluid in the right pleural cavity; the lower two-thirds of the right lung were obscured by a dense shadow. There were some moist râles over both lungs but especially on the right side. The hilar shadows were very dense. The roentgenological appearance of the left lung and of the upper portion of the right lung suggested miliary tuberculosis.

Case 6: (B. G. H. 4145) Forty year old colored female. Cause of death: tuberculous caries of the seventh and eighth dorsal vertebral bodies, with paravertebral abscesses and overwhelming miliary tuberculosis. (Plate 5)

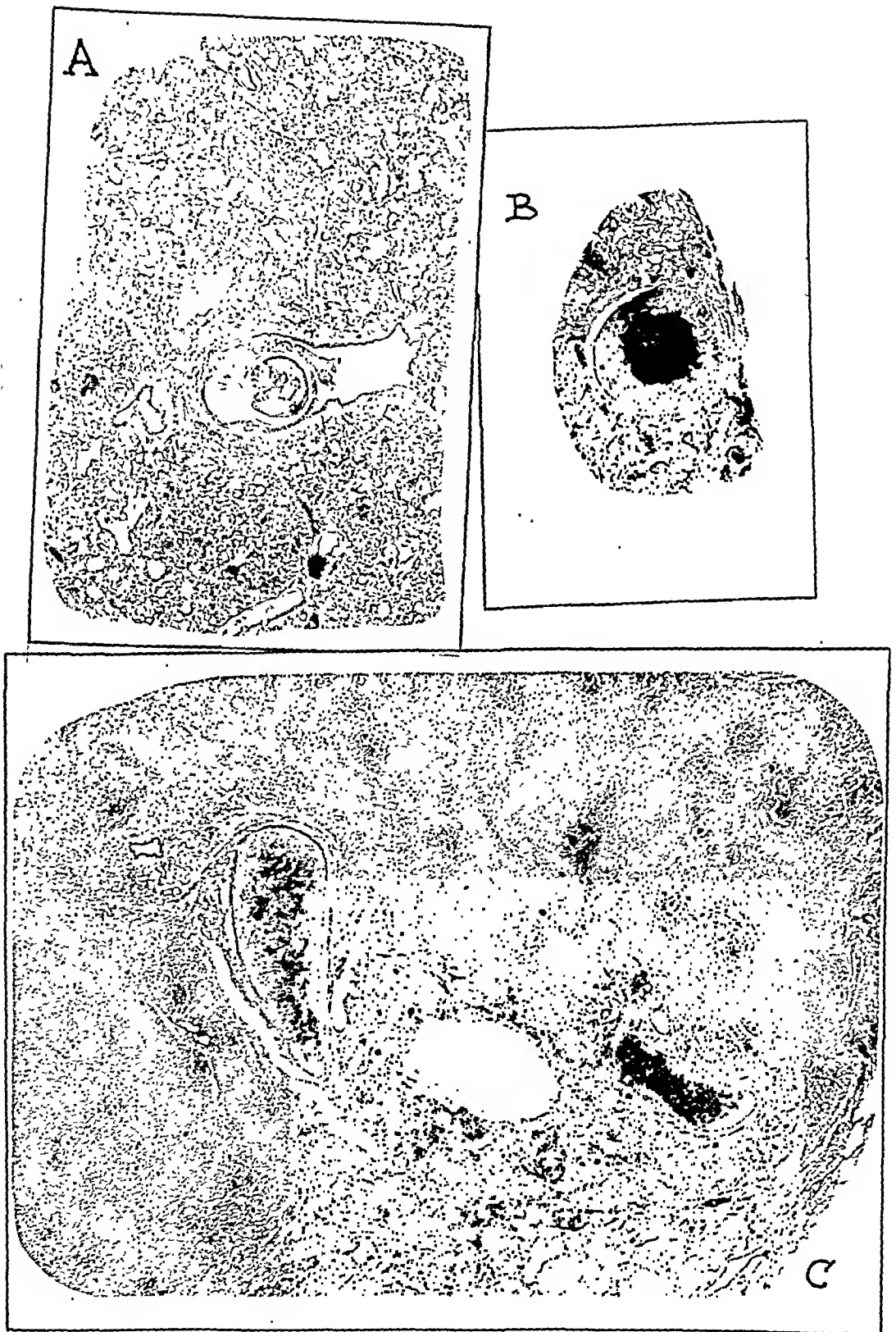


PLATE 5

This is a case of overwhelming miliary tuberculosis with unusually dense seeding throughout both lungs and with densely seeded miliary tubercles in the liver, spleen, kidneys and scattered miliary tubercles in the myocardium, the thyroid, the urinary bladder and a few pinhead-sized tubercles in the mucosa of the jejunum. The immediate source for this massive blood-stream infection was tuberculous caries of the seventh and eighth dorsal vertebral bodies, mostly within their ventral portions. Typical tuberculous paravertebral abscesses had formed at both sides of the spinal column, bulging toward the pleural cavities. The abscess on the right measured 3 x 3 cm., on the left 4 x 4 cm.; their sagittal diameter varied between 0.5 and 1 cm. Their content was frank pus containing an exorbitant number of tubercle bacilli.

The only remnants of a primary tuberculous infection were two chalky subpleural lymph nodules, one at the interlobar surface of the left lower lobe slightly below the level of the major bronchus, the other very slightly above this level in the midportion of the left upper lobe. There was, in addition, a firmly calcified lesion deep in the parenchyma in the midportion of the left upper lobe. There was no other trace of any chalky or calcified lesion, neither in the remainder of both lungs nor in any of the bronchomediastinal lymph nodes. Mesenteric lymph nodes were entirely negative. Between the mediastinal border of the left upper lobe and the parietal pleura there were a few thin fibrous band adhesions. There was some anthracotic induration of a few bronchopulmonary lymph nodes at the hilum of the left upper lobe. All tracheobronchial, paratracheal, anterior mediastinal and angulus lymph nodes on both sides showed unusually marked tuberculous hyperplasia; they were considerably enlarged, varying in size between that of a cherry and a small date. The lymph nodes in the bifurcation, in addition, were about hen-egg sized, causing moderate compression of the lumen of the right major bronchus.

An attempt to explain the gross picture faced considerable difficulties. There was no primary complex in the usual sense of the word. The entire lung was fixed in formaldehyde and carefully sliced, but apart from dense miliary tuberculosis there were no further findings, especially no recent reinfection lesions. The three chalky or calcified structures and portions from all bronchomediastinal lymph nodes with the closely attached parts of the trachea and bronchi were examined, along with various parts of the pulmonary parenchyma and all organs in which gross tuberculous changes were noticed. Plate 5 shows some of these lesions. The firmly calcified structure in the midportion of the left upper lobe proved to be a typical calcified phlebolith with early bone formation (A). The unusually dense miliary tuberculosis with collateral inflammatory edema in the intervening alveoli is clearly noticeable in this picture. "B" shows one of the chalky subpleural lymph nodules which appeared well encapsulated by a fairly thick hyaline capsule, with the chalky material forming the core of the lesion. This picture shows the subpleural nodule found at the interlobar surface of the left upper lobe. There is only slight localized hyalinization in the parenchyma around this nodule. A similar picture was seen in the anthracotic lymph nodule of the left lower lobe just below the hilum level; there were a few cholesterol crystals in the chalky centre. All sections taken through the various portions of the lungs showed a uniform pattern of miliary tuberculosis of unusually massive dissemination. The seeding in the apices was not more marked than in any other part of both lungs. Most of the tubercles appeared already as small confluent

nodules and there was a great deal of large cellular exudate in the intervening alveoli. Many of the bronchioles were apparently obliterated by the growth of the hematogenous tubercles; they had disappeared in most of the sections. A few lymph nodes from the left upper tracheobronchial group showed, as grossly noticed, more marked anthracosis and a few hyaline nodules. As a whole, however, the histological picture in all bronchomediastinal nodes was uniformly the same, as shown in picture "C". There were confluent conglomerate tubercles with irregular caseation and recent epithelioid giant cell tubercles. As seen in photograph "C" there was contiguous extension of this process into the wall of the bronchus, the mucosa of which showed an abundance of Langhans' giant cells and typical epithelioid giant cell tubercles. This section was taken from the right major bronchus which, at gross inspection, appeared moderately compressed by the egg-sized lower tracheobronchial lymph node. Similar pictures, however, were found also in the more central parts of the major bronchus surrounded by the tuberculous lymph nodes of the upper tracheobronchial group.

We were not able to find a primary focus in this case. The two chalky subpleural lymph nodes pointed to the upper or midportion of the left lung as the site of the primary infection. In one of the regional left upper tracheobronchial lymph nodes there was marked anthracosis and hyaline nodular fibrosis, apparently of tuberculous nature. There was, in addition, a small anthracosilicotic nodule in this lymph node, close to the hyaline tubercles. The tuberculosis of the dorsal spine was, naturally, of hematogenous origin. The massive lymphogenous progression secondary to the overwhelming miliary tuberculosis of the lungs is somewhat unusual in our experience with cases of acute hematogenous dissemination. It serves, however, to lay stress on the acute progression of pulmonary lesions in general, regardless of whether their pathogenesis is blood-borne or air-borne. Also, it demonstrates a massive involvement of the tracheobronchial tubes contiguous to the acute lymph node tuberculosis without gross ulceration or erosion. This case, then, shows that most acute diffuse lymph node tuberculosis is not restricted to a primary infection, nor to so-called endogenous exacerbation, nor to true progressive reinfection. It can be just as marked and even more diffuse in lymph nodes draining lungs when they are the seat of an overwhelming hematogenous dissemination, apparently leading rapidly to massive intraalveolar and intrabronchiolar spread. The possibility that the massive tuberculosis of the lower tracheobronchial lymph nodes might be a more direct effect of lymphogenous extension from the para- and prevertebral tissue, including especially the parietal pleura, will be considered in our comment later.

The first symptoms of the tuberculous infection in this case were those of iritis, following an attack of severe cold with cough. This was three months previous to death. A few weeks later the patient became progressively weaker; there were night sweats and considerable nonproductive cough. Two weeks before she died there was increasing occipital headache with stiffness of the neck. The roentgenological diagnosis of the lungs was "diffuse fine mottling, as seen in miliary tuberculosis."

COMMENT

The striking difference in the anatomical findings of the 6 cases in this series and of those presented in the preceding papers on true reinfection is seen by a comparison of the respective charts. Apart from the remnants of the primary pulmonary complex the tuberculous lesions in the lungs are clearly of hematogenous nature in 4 out of our 6 cases. In one (no. 4), there was no postprimary involvement of the lungs whatsoever, and the first case is an exception in so far as endogenous exacerbation in one of the regional lymph nodes produced a perforation of the bronchial tube, followed by scattered intrabronchial aspiration tuberculosis. This complication of endogenous lymphoglandular exacerbation is, on the basis of our own experience, unusual. In the acute stages of progressive primary infections, however, particularly in children, it is not infrequent. The possible rôle of the tuberculin reaction in relation to this focal exacerbation of lymphoglandular tuberculosis regional to an obsolete primary focus has been briefly discussed in the text. The dissemination in our case was restricted to a few levels in both lungs, although there might have been a more diffuse spread, had the patient not succumbed to uremia. Extension of lymph node tuberculosis through the bronchial tube, however, is not necessarily followed by massive intrabronchial spread. This was learned not only from a few anatomical and clinical observations on "epituberculous pneumonia" (13), but—since that time—from one more bronchoscopic chance finding of in part caseated lymph node tissues in the major bronchus of a young white adult female. Apart from atelectasis in the homolateral lung, there was neither at that time nor since any clinical sign of progressive disease. The patient appeared in good health.

In the last 2 cases of our series the dissemination through the blood-stream is unusually massive, not only in the lungs but especially in such organs as spleen, liver and kidneys. The histological analysis of the pulmonary lesions in one of these cases, in particular, reveals a massive progressive miliary tuberculosis throughout the pulmonary parenchyma, gradually involving more and more air sacs and many bronchioli. The histological picture brought about by this dense miliary seeding within the pulmonary lobules is not unlike that seen in recent tuberculous bronchopneumonia caused by acute intrabronchial progression from a recent cavity. Alveoli and bronchioli between the densely placed miliary tubercles are filled with inflammatory edema fluid and many large mononuclear cells. There is, however, no caseation. Although the tuberculous process is thus spreading rapidly through the pulmonary parenchyma from all the innumerable hematogenous tubercles involving the intervening alveoli and many bronchioli, death from this massive overwhelming miliary tuberculosis and especially from the associated tuberculous meningitis apparently precludes the development of any further intrabronchial spread. It is the absence of the gross features of intracanalicular spread with acinous or peribronchitic tuberculous pneumonia, and even more so of cavities, recent or old, and of postprimary apical or subapical calcified tubercles and scars, which is common to all the 6 cases of our series. While the hematogenous character of the dense miliary tubercles in the last 2 cases was clear, presenting the well known picture

of overwhelming miliary seeding, 2 other cases (nos. 2 and 3) showed only sparsely scattered tubercles in the lungs, while other organs, such as the spleen and liver, contained very many tubercles. It is known from the anatomical findings in cases of so-called protracted hematogenous tuberculosis that the lungs show, at times, comparatively scattered involvement.

Anatomical findings in the bronchomediastinal lymph nodes, usually interpreted as endogenous lymphoglandular exacerbation or protracted lymphoglandular progression, are present in the first 4 cases of our series. In none of these are there any complicating postprimary pulmonary lesions which could be responsible for the active or reactivated tuberculosis in the bronchomediastinal lymph nodes. Only in the fifth case of our series, which is a typical example of protracted hematogenous tuberculosis following a comparatively late primary infection, it seemed impossible to attempt a pathogenetic analysis of the pulmonary lesions, complicated by an obviously chronic tuberculous pleuritis and tuberculosis of the peritoneum, in their relation to the more recent tuberculous changes in the lymph node component of the primary complex. Although the chalky-fibrous and somewhat calcified remnants of the primary infection, were surrounded by active tuberculous lesions in these lymph nodes, the lymph nodes draining the right lung showed the same degree of diffuse active tuberculosis. In addition, there was considerable miliary tuberculosis in both lungs from which still recent lymphogenous spread might have occurred to all bronchomediastinal lymph nodes, just as it was found in the periaortic and peripancreatic nodes. There was, however, no evidence of a true exogenous reinfection as the source for the massive tuberculous pleuritis, and for this reason it was felt that protracted lymphogenous tuberculosis in the lymph nodes of the primary complex was originally responsible for this extensive hematogenous tuberculosis.

As to the type of the primary lesions in these cases, there was distinct perifocal spread around the primary focus in 4 instances. In one of these in particular the location and extension of the calcified tubercles and fibrous scars resembled the late stages of a so-called primary subapical infiltration, as discussed in one of our preceding papers (14).

In the last case of our series the primary focus was not found. Only two subpleural, firmly chalky lymph nodules and a few small fibrous conglomerate tubercles in one regional bronchopulmonary lymph node pointed to the area in which the primary infection had taken place. In cases of overwhelming miliary tuberculosis, it has been found sometimes difficult, if not impossible, to locate the true primary lesion (Kudlich, Wells). This last case of our series showed, apart from the unusually massive miliary involvement of the lungs, also a most marked enlargement of all bronchomediastinal lymph nodes, but especially of those in the bifurcation angle. In our past experience we have hardly observed such extreme degrees of tuberculous hyperplasia with caseation—the lower tracheobronchial lymph nodes were hen-egg sized—in association with miliary tuberculosis of the lungs. The direct source for the massive miliary tuberculosis was clearly established in the recent tuberculous abscesses of the seventh and eighth dorsal vertebral bodies. These abscesses had extended

into the parietal pleura without, however, piercing through its surface. While the extrapleural paravertebral area is normally drained by the intercostal lymphatics which, before entering the thoracic duct, pass through prevertebral lymph nodules, the mediastinal portion of the parietal pleura is drained by lymph vessels which terminate in the posterior mediastinal lymph nodes. Some efferent channels of these nodes join the tracheobronchial lymph nodes (15, 16). There exist, then, direct connections through efferent vessels of the posterior mediastinal set of the prevertebral lymph nodes to the lower tracheobronchial lymph nodes. From these anatomical facts it appears that lymph vessels draining tuberculous pre- and paravertebral subpleural structures and the mediastinal portion of a tuberculous parietal pleura, some of which converge in the prevertebral set of the retromediastinal lymph nodes, can transmit the tuberculous infection through some efferent lymph vessels directly to the lower tracheobronchial lymph nodes before joining the thoracic duct. On the basis of the anatomical findings in our case 6 with the unusually massive tuberculous involvement of the lower tracheobronchial lymph nodes, extending downward to the level of the seventh and eighth vertebral bodies, one wonders whether this does not, at least in part, represent the direct result of the tuberculous paravertebral abscesses, leading through the retromediastinal lymph nodes to the bronchomediastinal lymph node chain below the bifurcation angle. We are considering such an interpretation because, in our past experience with anatomical findings of overwhelming miliary tuberculosis, the lymphogenous progression in the bronchomediastinal lymph nodes never had reached such an extreme degree as observed in the lower tracheobronchial group in our case. Also, the interlobar bronchopulmonary lymph nodes were involved to a considerably smaller extent in this case. As we have neglected to examine histologically the entire pre- and paravertebral structures with the retromediastinal lymph nodes (only small portions of the tuberculous vertebral bodies, especially including the periosteum, were studied microscopically, showing unusually marked recent caseation) we feel the more that it should be of great interest to examine in future cases of acute tuberculous destruction of the lower thoracic spine, in connection with overwhelming hematogenous seeding, any possible routes of direct extension through the retromediastinal lymph nodes. Another unusual finding in this case was the apparent direct and fairly massive tuberculous spread from the tracheobronchial lymph nodes into the contiguous bronchial walls, the mucosa of which was studded with recent tubercles. While in many sections this contiguous spread seemed caused by the encroachment from the markedly enlarged tuberculous lymph nodes, there were also miliary tubercles seen in the walls of various bronchi without direct connection with the lymph node capsule. These could have resulted also from direct hematogenous dissemination through the bronchial arterial system.

SUMMARY

The anatomical findings in 6 cases of primary protracted tuberculosis in adults are discussed. Their ages varied from seventeen to seventy-five years. Four, or possibly 5 of these represent changes of "endogenous lymphoglandular

reinfection" with hematogenous dissemination involving especially spleen, liver, kidneys, the lungs, the pleura, peritoneum and leptomeninges. The pulmonary lesions, when present, are clearly of hematogenous character, either of the overwhelming miliary type (in 2) or with more sparsely scattered miliary and small nodular tubercles (in 2) without further intrabronchial spread. In one case this "lymphoglandular reinfection" produced an acute softening, causing perforation of the bronchial tube, with restricted recent aspiration tuberculosis. The primary lesions were either entirely obliterated or in a state of advanced healing. In the more centrally located lymph node components of the primary complex a combination of older, chronic and recent tuberculous changes was seen, usually designated as lymphogenous-endogenous reinfection. The terms "endogenous exacerbation" or "protracted lymphoglandular progression" appear preferable.

A comparison of the entire anatomical picture in these cases with that seen in exogenous reinfection shows that the pulmonary lesions are clearly of hematogenous character and that they do not lead to further intrabronchial progression as seen in the common type of pulmonary tuberculosis.

One instance of acute miliary tuberculosis with overwhelming dissemination in the lungs is included, with caseated liquefaction of two lower thoracic vertebral bodies and tuberculous paravertebral abscesses, extending into the parietal pleura, as its source. The unusually massive tuberculous hyperplasia of the lower tracheobronchial lymph nodes found in this case is suggestive of a direct lymphogenous involvement through efferent channels from the prevertebral retromediastinal nodes to the lower tracheobronchial group, apart from massive spread from the overwhelming miliary dissemination through the lungs.

The literature dealing with "endogenous-lymphogenous reinfection" is critically analyzed. No unequivocal proof has been presented that in the development of the common (phthisic) form of pulmonary tuberculosis this endogenous lymphoglandular exacerbation is of pathogenetic significance. It can lead, however, to acute or protracted hematogenous dissemination in various organs, including the lungs and the leptomeninges, especially in the presence of recent caseation with cavitation in bronchomediastinal or angulus lymph nodes, in orthograde direction to the obsolete primary focus.

SUMARIO

Preséntanse los hallazgos anatómicos en 6 casos de tuberculosis prolongada primaria en adultos de 17 a 75 años de edad. Cuatro, o posiblemente 5, manifestaban alteraciones de "reinfeción linfoganglionar endógena," con diseminación hematógena que interesaba en particular el bazo, hígado, riñones, pulmones, pleura, peritoneo y leptomeninges. Cuando había lesiones pulmonares eran netamente hematógenas, bien del tipo granulicó agobiador (en 2) o con tubérculos nodulares pequeños y miliars más esparcidos (en 2) sin más propagación intra-bronquial. En un caso esta "reinfeción linfoganglionar" produjo reblandecimiento agudo, ocasionando perforación bronquial, con una limitada tuberculosis reciente por aspiración. Las lesiones primarias estaban o bien completamente borradas o en estado de cicatrización avanzada. En los componentes linfo-

ganglionares del complejo primario más centralmente localizados observóse una combinación de alteraciones tuberculosas antiguas, crónicas y recientes, denominada habitualmente reinfección linfo-endógena, aunque parecen preferibles los términos de "exacerbación endógena" o "evolución linfoganglionar prolongada."

Una comparación del cuadro anatómico total en estos casos con el observado en la reinfección exógena revela que las lesiones pulmonares son netamente hematógenas y que no conducen a mayor propagación intrabronquial como sucede en el tipo corriente de la tuberculosis pulmonar.

También se describe un caso de granulia aguda con diseminación agobiadora en los pulmones, y licuación caseada de los cuerpos de las dos vértebras torácicas inferiores, teniendo como foco de origen, abscesos paravertebrales tuberculosos que se extienden a la pleura parietal. La extraordinaria hiperplasia tuberculosa masiva de los ganglios linfatraqueobronquiales inferiores en este caso indica invasión linfógena directa a través de los conductos eferentes de los ganglios retromediastínicos prevertebrales al grupo traqueobronquial inferior, aparte de la difusión masiva procedente de la agobiadora diseminación granúlica a través de los pulmones.

Analizada críticamente la literatura relativa a la "reinfección endolinfógena," no se encontraron datos positivos de que en el desarrollo de la forma habitual (tísica) de la tuberculosis pulmonar revista importancia patogenética esa exacerbación linfoganglionar endógena. Puede sí conducir a diseminación hematógena aguda o bronquial a varios órganos, incluso los pulmones y las leptomeninges, sobre todo en presencia de caseación reciente con cavitación en los ganglios linfáticos broncomediastínicos, o angulares, en dirección ortógrada al foco primario anticuado.

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EOSINOPHILIA IN SILICOSIS¹

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A series of patients with eosinophilia have been encountered here in the past for which no cause could be determined.

Aside from diseases of the hematopoietic system which form a rare group in which the eosinophil count is increased, there is a second group in which the majority of eosinophilias occur. This group includes allergic diseases (bronchial asthma, hay fever, urticaria), parasitic infestations and skin diseases. They were ruled out as possible causes in this series.

While the patients with unexplained eosinophilia were being studied the impression arose that a preponderant number were coal miners many of whom had silicosis and silico-tuberculosis. Because a diligent search of the literature failed to reveal any mention of eosinophilia in coal miners or its association with silicosis, it was decided to test the validity of this impression.

MATERIAL

The sanatorium records of 813 male patients admitted in a recent two-year period were reviewed. All essential data were tabulated and analyzed. During that time, there were 654 nonminers and 159 miners admitted. Twenty-five of the 159 miners and 72 of the 654 nonminers were eliminated from the study because of heart disease, diabetes, cancer, incomplete records and the presence of eosinophilia with a known cause, leaving a total of 134 miners and 582 nonminers. The 582 nonminers were used as a control group.

Miners and nonminers were classified as shown in table 1 and the incidence of eosinophilia determined for each group. The tuberculosis, silico-tuberculosis and silicosis groups were further divided (table 2) into first, second and third stage subgroups, according to the extent of disease. The average eosinophil count for each stage of disease was calculated (table 3) to ascertain what relationship, if any, existed between the eosinophil count and the extent of the disease. All eosinophil counts over 300 cells per cubic millimeter were considered abnormal. In estimating the number of eosinophils, at least 300 leucocytes were counted on every differential count.

RESULTS

The accompanying tables need little explanation. From a statistical standpoint, except for the nonminer control group, the groups are not numerically large. But in view of a 51.2 per cent incidence of eosinophilia in coal miners with silicosis, as well as a 32.4 per cent incidence in coal miners with silico-tuberculosis compared to a 16.1 per cent incidence in miners with tuberculosis and a 5.9 per cent incidence in the control group, it seems safe to conclude that eosinophilia is frequent in patients with silicosis. Even though eosinophilia is not a

¹ From the Pinecrest Sanitarium (West Virginia State Tuberculosis Sanitarium), Beckley, West Virginia.

TABLE 1

Incidence of unexplained eosinophilia in miners and nonminers

Miners.....	134	
Miners with unexplained eosinophilia.....	42	31.3%
Miners with silicosis.....	41	
Miners with silicosis and unexplained eosinophilia.....	21	51.2%
Miners with silico-tuberculosis.....	37	
Miners with silico-tuberculosis and unexplained eosinophilia.....	12	32.4%
Miners with tuberculosis.....	56	
Miners with tuberculosis and unexplained eosinophilia.....	9	16.1%
Nonminer males with tuberculosis.....	582	
Nonminer males with tuberculosis and unexplained eosinophilia.....	34	5.9%

TABLE 2

Distribution of patients according to extent of disease

	FIRST STAGE DISEASE	SECOND STAGE DISEASE	THIRD STAGE DISEASE
Miners with silicosis (41).....	12	18	11
Miners with silico-tuberculosis (37).....	None	24	13
Miners with tuberculosis (56).....	9	19	28
Nonminers with tuberculosis (582).....	67	174	341

TABLE 3

Relation of average eosinophil count to the extent of disease

	AVERAGE COUNT IN FIRST STAGE DISEASE	AVERAGE COUNT IN SECOND STAGE DISEASE	AVERAGE COUNT IN THIRD STAGE DISEASE	GENERAL AVERAGE FOR ALL STAGES
Miners with silicosis.....	322	634	652	536
Miners with silico-tuberculosis.....	No cases	503	512	508
Miners with tuberculosis.....	277	178	239	231
Nonminers with tuberculosis.....	159	127	171	152

TABLE 4

Comparison of the number of patients in each group with no eosinophils on differential leukocyte count

	NO EOSINOPHILS ON DIFFERENTIAL COUNT	
	Number of patients	Percentage
Miners with silicosis (41).....	3	7.3
Miners with silico-tuberculosis (37).....	5	13.5
Miners with tuberculosis (56).....	12	21.4
Nonminers with tuberculosis (582).....	213	36.5

constant finding in silicosis, it occurs in a sufficiently high percentage of patients to suggest the existence of a relationship which is not casual.

Further evidence of this relationship is found in table 3 which shows the average eosinophil counts in the three stages of disease. The counts vary little between the second and third stage of silicosis but differ significantly from the first stage. In addition, the counts are above normal in the silico-tuberculosis group. The highest individual count in the first stage silicosis group was 832 per cu. mm.; in the second stage 1,672 per cu. mm.; and in the third stage 2,013 per cu. mm. The 2,013 eosinophils per cu. mm. represent a 21 per cent eosinophilia. Thus, the average count and the highest count for each stage of silicosis are proportional to the extent of the disease. This also is true of the silico-tuberculosis subgroups but does not obtain in the other subgroups.

Comparison of the number of patients in each major group, who had no eosinophils on differential leucocyte count, is shown in table 4. Only 3, or 7.3 per cent, of the 41 miners with silicosis failed to show eosinophils in contrast to 213, or 36.5 per cent, of 582 nonminers.

There was no correlation between the age of the patient or the length of service in the mines and the eosinophil count. An explanation for this is the fact that the concentration of silica dust varies greatly in different mines because the amount of stone varies which must be drilled, cut, crushed and removed in order to make the coal accessible. For that reason, the miners in one mine may develop silicosis after a few years' work while the miners in another mine may never develop the disease.

DISCUSSION

Eosinophilia is most often a manifestation of a generalized allergic response. Its presence in silicosis suggests that silica might be considered an allergen but it is improbable that an inert substance such as silica could produce an allergy. Furthermore, eosinophilia occurs in several conditions not related to allergy and its association with silicosis is additional evidence that it is not always associated with allergic phenomena.

It is well known that coal dust alone is incapable of producing a tissue reaction; therefore, it can be disregarded as a cause for eosinophilia.

An explanation of the eosinophilia, which is not without objection, is to be found in the experimental work of Chillingworth *et al.* (1) who, by the use of an intratracheal ball-valve which partially obstructed expiration but not inspiration, produced emphysema and an asthmatic syndrome with eosinophilia as high as 18 per cent in dogs. Also, they produced dyspnea with an average eosinophilia of 7.19 per cent in several medical students, using a partially blocked oral flutter valve which caused expiratory resistance. They concluded that the eosinophilia was due to expiratory delay when accompanied by alveolar overdistention and was of a specific nature.

Pescatori (2) produced eosinophilia by asphyxiating rabbits with carbon dioxide gas and concluded that acidosis was the cause. Chillingworth *et al.* objected to the acidosis theory on the ground that the eosinophilia was due to alveolar overdistention and expiratory delay and not to acidosis. Even so, there is an obvious relationship, namely acidosis, between Pescatori's and Chillingworth's methods of producing eosinophilia. Whether oxygen is excluded

from the lungs by the substitution of another gas for air or by a mechanical obstruction, acidosis results just the same. Regardless of this relationship, it is unlikely that acidosis is in any way related to eosinophilia. The chief objection to the acidosis theory is that there are numerous diseases in which acidosis occurs but which never show an eosinophilia.

Even though silicosis and asthma have a totally different etiology, they do have several features in common. Silicosis produces irreparable anatomical and physiological changes in the lungs. The essential structural changes consist of fibrosis, emphysema and a reduction in the pulmonary capillary bed. The functional alterations which lead to a low pulmonary reserve are a decrease in vital capacity, an increase in residual air, a high alveolar carbon dioxide tension with a low oxygen tension and a subnormal oxygen saturation of the blood. Moreover, the alterations in respiratory physiology in silicosis are virtually the same as in asthma with the possible exception of bronchospasm and there is evidence that bronchospasm, though not a constant feature, does occur in silicosis. The partial and temporary relief of dyspnea in some patients with silicosis following the administration of such bronchodilating drugs as epinephrine and ephedrine is clinical evidence that bronchospasm plays a part in the dyspnea of silicosis.

In addition to the physiological changes, emphysema is common to both silicosis and asthma. An obstructive type of emphysema occurs in asthma due to bronchospasm, whereas a compensatory type occurs in silicosis which is the result of fibrosis. Irrespective of the bronchospasm and the far different basic cause for the emphysema in asthma and silicosis, alveolar overdistention and expiratory delay are essential factors in both asthma and silicosis. In asthma these factors are more prominent and the difference is one of degree only.

Emerson (3) lists emphysema among the causes of eosinophilia but cites only one case. Other more recent texts on hematology do not mention it. Obviously others either have not made the observation or have been unable to verify it. Chillingworth *et al.* mentioned but rejected emphysema in the consideration of causes for eosinophilia in their experiments. Their objection was based on the fact that the eosinophilia disappeared in one of their dogs following spontaneous extubation after permanent emphysema had developed. It would have been worth while to remove the tracheal valves in all 7 dogs to determine whether or not the disappearance of the eosinophilia was an invariable consequence of the removal of the valve. A single observation does not justify the rejection of emphysema as the cause for the eosinophilia.

Emphysema of the degree produced in dogs by mechanical obstruction is seldom seen in human beings because no parallel clinical condition exists except for the rare obstruction which occurs in tumors of the trachea or larynx. However, the emphysema produced by mechanical obstruction is not the only type of emphysema with which eosinophilia is associated. That fact is amply supported by the results herein reported which not only confirm but extend Emerson's original observation.

Emphysema is not seen, usually, in tuberculosis except in the rare far advanced fibroid type in which there has been fibrous replacement and contraction

of a large portion of one or both lungs with consequent compensatory emphysema of the remaining portion. Too few cases of this type have been seen to warrant a conclusion regarding the presence or absence of eosinophilia, but it is reasonable to assume that eosinophilia should accompany this type of disease.

SUMMARY AND CONCLUSIONS

A statistical analysis of the records of 134 miners and 582 nonminers was made which confirms the impression that eosinophilia occurs frequently in patients with silicosis.

The incidence of eosinophilia in 41 miners with silicosis was 51.2 per cent; in 37 miners with silico-tuberculosis 32.4 per cent; in 56 miners with tuberculosis 16.1 per cent; in 582 nonminers with tuberculosis 5.9 per cent.

The eosinophil counts were found to be proportional to the extent of silicosis and emphysema. In the first stage of silicosis the highest count was 832 cells per cu. mm. and the average count 322 cells per cu. mm.; in the second stage the highest count was 1,672 cells and the average was 634 cells; in the third stage the highest count was 2,013 cells and the average 652 cells. No such correlation was noted in patients with tuberculosis.

The etiology of the eosinophilia in silicosis was discussed.

It is believed that the evidence presented justifies the conclusion that the eosinophilia in silicosis is due to emphysema and its invariable consequents, alveolar distention and expiratory delay.

SUMARIO Y CONCLUSIONES

Un análisis estadístico de los protocolos de 134 mineros y de 582 personas que no se dedican a la minería confirma la impresión de que existe eosinofilia frecuentemente en los enfermos de silicosis.

La incidencia de la eosinofilia representó: en 41 mineros con silicosis 51.2%; en 37 mineros con silico-tuberculosis 32.4%; en 56 mineros con tuberculosis 16.1%; en 582 no mineros con tuberculosis 5.9%.

El número de eosinófilos es proporcional a la extensión de la silicosis y el enfisema. En el primer período de la silicosis la numeración máxima es de 832 células por mm. cu. y el promedio 322 por mm. cu.; en el segundo período las cifras respectivas fueron 1,672 y 634; y en el tercero 2,013 y 652. No se observó una correlación semejante en los tuberculosos.

Discútese también aquí la etiología de la eosinofilia en la silicosis.

El A. opina que los datos presentados justifican la conclusión de que la eosinofilia en la silicosis procede del enfisema, teniendo como consecuencia general, distensión alveolar y tardanza en la espiración.

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TUBERCULOSIS OF THE TONGUE¹

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Most authors who have written on this subject begin their articles with the statement that tuberculosis of the tongue is an uncommon or infrequent condition. This does not seem to be wholly borne out, because a review of the literature shows quite a number of cases. Possibly the conjecture by most authorities is true, that if tuberculous patients were more carefully examined during life and postmortem, many more cases of lingual tuberculosis would be found. The literature from 1920 to 1942 contains many reports of tuberculosis of the tongue, but no articles were published on this subject during 1942 and 1943. The total number of reported cases seems to be slightly more than 400.

Morgagni described the lesion of tuberculosis of the tongue in 1761 and Virchow reported the first autopsied case. Many other reports have appeared since then. Tuberculosis of the tongue is caused by the lodgment of tubercle bacilli in the tissues of the tongue and their subsequent proliferation (3). The primary etiological factors are the virulence of the organisms and local tissue resistance. The tongue of practically every patient with active pulmonary tuberculosis is continuously exposed to bacilli-laden sputum (7). The relative infrequency of tuberculosis of the tongue is probably due to the thickness of the mucous membrane and the marked general resistance of striated muscle to bacterial invasion. The mechanical cleansing effect of saliva and the continual movement of the tongue undoubtedly play some part.

There are several types of lesions: (1) ulcers, (2) fissures, (3) granulomata, (4) tuberculomata and (5) glossitis. Of these, the ulcer is the most frequent. There is no definite site of predilection though the lateral margins and the tip are more commonly involved.

The symptoms of tuberculosis of the tongue are variable. Pain is usually late, occurring only after the infection progresses. This pain is severe, unremittent and progressive.

Treatment is mainly palliative, since the majority of cases are in the terminal stage of the pulmonary disease. In early cases, excision followed by cauterization, or initial cauterization of the lesion may effect a cure. In terminal cases the application of local anesthetic agents may afford some relief, though at times it may be necessary to resort to injection of the lingual nerves with alcohol to control the pain.

I wish to report 30 cases which occurred at the Veterans Administration, Oteen, North Carolina from January 1, 1938 to August 1, 1944. In 7 of these the diagnosis was proved by biopsy.

In this series, 28 cases were classified on admission as far advanced in regard to their pulmonary condition. The lesion of the tongue healed in 8, but 4

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² Major, M.C., A.U.S. Veterans Administration, Tucson, Arizona.

succumbed to the disease of the lung. Fourteen patients did not show any improvement and died within five days to five months after the diagnosis of tuberculosis of the tongue had been made. One patient did not show any improvement of the tongue and one showed improvement at the time he left the hospital. Two cases were classified on admission as moderately advanced and in both the lingual lesions healed. Recurrences were noted in 2 patients with far advanced tuberculosis. In one the tongue healed for a second time and in the other the lesion progressed until death occurred from the pulmonary disease.

Binstok (2) states that statistics show that cases of tuberculosis of the tongue form approximately 50 per cent of all cases of tuberculosis of the oral cavity. The incidence of tuberculosis of the tongue has been given as from a small fraction of one per cent to 19.6 per cent. The incidence at this hospital covering 8,204 admissions from January 1, 1938 to August 1, 1944 is 0.25 per cent. Of the 8,204 admissions, 6,244 were white and 1,960 were colored. Twenty-six of the cases of lingual involvement occurred in white patients and 4 in colored, a ratio of approximately 6 to one. This is in contrast to the statement by Katz (7) that this condition is only slightly less frequent in colored than in the white race and to the absence of any cases in the colored race in the report by Finney (6). As late as 1940 Baron (1) stated that apparently no instance of tuberculosis of the tongue had been recorded in Negroes. No cases of tuberculosis of the tongue were found in females, but these comprised only 139 admissions.

The majority of the cases occurred during the fourth decade of life, there being 20, or 66.6 per cent; 20 per cent or 6 cases were in the third decade. This is in accordance with the findings of Baron (1), D'Aunoy (3), Farber (5) and Finney (6), but in contrast to those of Katz (7) and Morrow (10), the greater number of whose cases were in the third decade.

The most common manifestation of the lesion was an ulcer, which occurred in 93.4 per cent. The site was on the edge of the tongue in 40 per cent, on the base and tip in 26 per cent each and on the dorsum in 6 per cent. This is in agreement with the majority of previous reports.

All our cases except one had positive sputum. Sixteen of the cases, or 53 per cent, had associated tuberculous laryngitis and 11 or 36 per cent had oral and pharyngeal tuberculosis. There were 3 patients with gastro-intestinal tuberculosis, or 10 per cent. Other complications included 2 cases with tuberculous epididymitis and one each with tuberculous meningitis, tuberculous arthritis and tuberculous cystitis.

SUMMARY

Thirty previously unreported cases of tuberculosis of the tongue have been discussed. The incidence of this condition in a tuberculosis hospital has been considered, as well as various other complications.

SUMARIO

Discútese 30 casos de tuberculosis de la lengua inéditos hasta ahora, y considérase la incidencia de este estado en un hospital para tuberculosos, así como de otras varias complicaciones.

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FOUNDERS OF THE NATIONAL TUBERCULOSIS ASSOCIATION

An Historical Study

ROBERT G. PATERSON¹

One of the basic lists in connection with the history of the National Tuberculosis Association² is that of the founders³ of the movement. It is now forty-one years since the founding of the National Tuberculosis Association took place. As time passes it will become more and more difficult to secure information concerning some of these founders.

According to the minute book,⁴ kept so faithfully by Henry Barton Jacobs, M. D., and now in the Archives of the National Tuberculosis Association, there were 195 founders.⁵ Out of this total there were 185 who have been identified as physicians, 8 were laymen and 2 are undetermined.⁶ The distribution by states shows that 45 were residents of Pennsylvania; 33 of New York; 16 of Maryland; 12 of Massachusetts; 11 of Illinois; 9 of Colorado; 8 each of Connecticut and District of Columbia; 6 each of New Jersey and Ohio; 5 each of the Dominion of Canada and Rhode Island; 4 of Vermont; 3 of North Carolina; 2 each of California, Delaware, Georgia, Indiana, Maine, Michigan, Minnesota, Missouri and New Mexico; one each of Idaho, Louisiana, South Carolina, Virginia, Washington and Wisconsin. In the main, the distribution of the founders by states follows the historical development of interest in tuberculosis in point of time and place.

A further examination of this list reveals some interesting facts. At this date (July 1, 1945) there are 43 founders still living. Out of the 195 founders,

¹ Secretary, Committee on Archives, National Tuberculosis Association.

² On June 6, 1904, the Constitution and By-laws were adopted. The name selected was *National Association for the Study and Prevention of Tuberculosis*. On March 16, 1918, the Board of Directors voted to change the name to the *National Tuberculosis Association* and on June 7, 1918, the members of the Association voted to approve the action of the Board of Directors.

³ A founder is defined as one who attended any or all of the three meetings which led to the organization of the Association. These meetings are designated, as follows:

- | | | |
|---------------------|----------------------------|--------------|
| 1. January 28, 1904 | Baltimore, Maryland | Discussion |
| 2. March 28, 1904 | Philadelphia, Pennsylvania | Action |
| 3. June 6, 1904 | Atlantic City, New Jersey | Organization |

⁴ Minutes of the National Tuberculosis Association 1904-1905. Committees on Organization: Organization meeting, Executive Committee and Board of Directors. 109 pp.

⁵ On the occasion of the twenty-fifth anniversary meeting, a list of founders was published in the program and included 197 names. This list included the names of Norman Bridge, M.D. (1844-1925), Los Angeles, California and Matthew Munn Smith, M.D. (1864-1924), Austin, Texas. Neither of these men are listed as having attended any one of the three meetings and, therefore, are not considered as founders. However, they were elected to the first Board of Directors.

⁶ These two are probably laymen since the medical sources fail to record them. They are Charles P. Fry, New York City and Charles M. Lewis, Philadelphia. We have been unable to secure any information. If any of our readers have information, it would be appreciated if such would be sent to the author.

only 6 attended all three meetings⁷; 38 attended the first meeting; 66 the second meeting and 156 the third meeting. Eighteen⁸ of the founders have been elected president of the Association; 3 have served as secretary,⁹ and 6 have been the recipients of the Trudeau Medal.¹⁰

As one reviews the literature of tuberculosis from 1882 to 1904, the yeoman work of a relatively small group of these founders is strikingly revealed. The repetition of their names in connection with papers and discussions on tuberculosis occurs regularly in the sessions of the American Medical Association, the American Public Health Association, the American Climatological Association, the American Congress on Tuberculosis and the American Anti-Tuberculosis League. It was this group of earnest workers which made possible the founding of the National Tuberculosis Association.

The listing of the Founders of the National Tuberculosis Association gives the full name, alphabetically arranged; the year of birth and death, if such is the case; the place of residence at the time of registration and the meeting or meetings attended.

FOUNDERS OF THE NATIONAL TUBERCULOSIS ASSOCIATION

<i>Names</i>	<i>Birth and Death</i>	<i>Place of Residence</i>	<i>Meetings</i>
Adami, John George, M.D.	(1862-1926)	Montreal, Canada	(1) — —
Anders, Howard Schultz, M.D.	(1866+)	Philadelphia, Pa.	— (2) —
Anders, James Meschter, M.D.	(1854-1936)	Philadelphia, Pa.	— (2) —
Angney, William Muir, M.D.	(1860-1906)	Philadelphia, Pa.	(1) (2) —
Babcock, Robert Hall, M.D.	(1851-1930)	Chicago, Ill.	(1) — (3)
Baker, Henry Brooks, M.D.	(1837-1920)	Lansing, Mich.	— — (3)
Baldwin, Edward Robinson, M.D.	(1864+)	Saranac Lake, N. Y.	— — (3)
Barlow, Walter Jarvis, M.D.	(1868-1937)	Los Angeles, Calif.	— — (3)
Barnes, Noble Price, M.D.	(1871-1933)	Washington, D. C.	— — (3)
Barrier, John Marion, M.D.	(1860-1922)	Delhi, La.	— — (3)
Bergtold, William Harry, M.D.	(1865-1936)	Denver, Colo.	— — (3)
Beyer, Adm. Henry Gustav, M.D.	(1850-1918)	Washington, D. C.	— (2) (3)
Biggs, Hermann Michael, M.D.	(1859-1923)	New York, N. Y.	— (2) (3)
Black, John Janvier, M.D.	(1837-1909)	New Castle, Del.	— (2) —
Billings, Frank, M.D.	(1854-1932)	Chicago, Ill.	— — (3)
Blumenthal, Oliver Aaron, M.D.	(1870-1905)	Syracuse, N. Y.	— (2) —
Bonney, Sherman Grant, M.D.	(1864-1942)	Denver, Colo.	— — (3)
Bowditch, Vincent Yardley, M.D.	(1852-1929)	Boston, Mass.	(1) (2) (3)
Bracken, Henry Martyn, M.D.	(1854-1938)	St. Paul, Minn.	(1) — —

⁷ These were: Drs. Bowditch, Jacobs, Knopf, Minor, Osler and Welch.

⁸ These were: Drs. Trudeau (1904-5); Biggs (1905-7); Billings (1907-8); Bowditch (1908-9); Janeway (1909-10); Welch (1910-11); Ravenel (1911-12); Lowman (1913-14); Kober (1914-15); Baldwin (1916-17); Minor (1917-18); Lyman (1918-19); Vaughan (1919-20); Miller (1921-22); Brown (1922-23); Hatfield (1924-25); Sewall (1926-27); Taylor (1927-28).

⁹ These were: Drs. Jacobs (1904-20); Kober (1921-27); and Hatfield (1928+). As will be seen, these 3 men have served as secretary throughout the current life of the Association.

¹⁰ These were: Drs. Baldwin (1927); Sewall (1930); Brown (1933); Hatfield (1937); Lyman (1943); and Miller (1944). The Trudeau Medal was created by resolution of the Board of Directors, January 24, 1925, and the first recipient was Dr. Theobald Smith in 1926. Awards have been made annually since that date.

FOUNDERS OF THE NATIONAL TUBERCULOSIS ASSOCIATION—*Continued*

<i>Names</i>	<i>Birth and Death</i>	<i>Place of Residence</i>	<i>Meetings</i>
Brannan, John Winters, M.D.	(1853-1936)	New York, N. Y.	— — (3)
Brinton, Ward, M.D.	(1873-1935)	Philadelphia, Pa.	— — (3)
Brooks, Myron Joel, M.D.	(1868-1937)	New Canaan, Conn.	— (2) —
Brown, Lawrason, M.D.	(1871-1937)	Saranac Lake, N. Y.	(1) — (3)
Bryce, Peter Henderson, M.D.	(1853-1932)	Montreal, Canada	(1) — —
Bullock, Earl Sprague, M.D.	(1871-1941)	Silver City, N. M.	— — (3)
Carrington, Paul Miles, M.D.	(1862+)	Fort Stanton, N. M.	— — (3)
Casselberry, William Evans, M.D.	(1858-1916)	Chicago, Ill.	— — (3)
Caverly, Charles Solomon, M.D.	(1856-1918)	Rutland, Vt.	— — (3)
Clapp, Herbert Codman, M.D.	(1846-1929)	Boston, Mass.	— (2) —
Clark, Colin Reed, M.D.	(1869+)	Youngstown, Ohio	— — (3)
Cohen, Jacob Solis, M.D.	(1838-1927)	Philadelphia, Pa.	— (2) (3)
Coleman, Thomas Davies, M.D.	(1865-1927)	Augusta, Ga.	— — (3)
Coplin, William Michael Late, M.D.	(1864-1928)	Philadelphia, Pa.	— (2) —
Craig, Frank Ardary, M.D.	(1876+)	Philadelphia, Pa.	— (2) (3)
Curtin, Roland Gideon, M.D.	(1839-1913)	Philadelphia, Pa.	— — (3)
Cushing, Harvey, M.D.	(1869-1939)	Baltimore, Md.	— — (3)
Daland, Judson, M.D.	(1860-1937)	Philadelphia, Pa.	— — (3)
Darlington, Thomas, M.D.	(1858+)	New York, N. Y.	(1) — —
Davis, Nathan Smith, Jr., M.D.	(1858-1920)	Chicago, Ill.	— — (3)
Davisson, Alexander Heron, M.D.	(1869-1944)	Philadelphia, Pa.	— (2) —
Detwiler, Benjamin Horning, M.D.	(1831-1910)	Williamsport, Pa.	— (2) —
Devine, Prof. Edward Thomas	(1867+)	New York, N. Y.	— — (3)
Dinnen, James Michael, M.D.	(1856+)	Fort Wayne, Ind.	— — (3)
Doty, Alvah Hunt, M.D.	(1854-1934)	New York, N. Y.	— (2) (3)
Dunham, Henry Bristol, M.D.	(1872+)	Rutland, Mass.	— — (3)
Edson, Carroll Everett, M.D.	(1866-1930)	Denver, Colo.	— — (3)
Egan, James Andrew, M.D.	(1859-1913)	Springfield, Ill.	(1) — —
Ellenberger, John Wesley, M.D.	(1858-1931)	Harrisburg, Pa.	— (2) (3)
Elliott, Jabez Henry, M.D.	(1873-1942)	Toronto, Canada	(1) — —
Ellis, Charles Manly, M.D.	(1838-1911)	Elkton, Md.	— — (3)
Elsner, Henry Leopold, M.D.	(1857-1916)	Syracuse, N. Y.	— — (3)
Fetterman, Wilfrid Bernard, Jr., MD.	(1877+)	Philadelphia, Pa.	— (2) (3)
Fisher, Prof. Irving	(1867+)	New Haven, Conn.	— — (3)
Fisk, Samuel Augustus, M.D.	(1856-1915)	Denver, Colo.	— — (3)
Flick, Lawrence Francis, M.D.	(1856-1938)	Philadelphia, Pa.	— (2) (3)
Forchheimer, Frederick, M.D.	(1853-1913)	Cincinnati, Ohio	— (2) —
Ford, William Webber, M.D.	(1871-1941)	White Water, Mo.	(1) — (3)
Foster, John Pierrepont Codington, M.D.	(1847-1910)	New Haven, Conn.	— — (3)
Freudenthal, Wolff, M.D.	(1858-1930)	New York, N. Y.	(1) — —
Fry, Charles P.	(no. inf.)	New York, N. Y.	— — (3)
Fulton, John Samuel, M.D.	(1859-1931)	Baltimore, Md.	(1) — (3)
Gaylord, Charles Woodward, M.D.	(1846-1918)	Branford, Conn.	— — (3)
Gerhard, George Smith, M.D.	(1849-1920)	Ardmore, Pa.	— — (3)
Getchell, Albert Colby, M.D.	(1857+)	Worcester, Mass.	— (2) (3)
Gichner, Joseph Enoch, M.D.	(1864+)	Baltimore, Md.	(1) — (3)
Goepp, Rudolph Max, M.D.	(1866+)	Philadelphia, Pa.	— — (3)
Goler, George Washington, M.D.	(1864-1940)	Rochester, N. Y.	— — (3)
Goudiss, Charles Houston	(1880+)	Philadelphia, Pa.	— — (3)
Hackenburg, William Bower	(1837-1918)	Philadelphia, Pa.	— (2) —

FOUNDERS OF THE NATIONAL TUBERCULOSIS ASSOCIATION—*Continued*

<i>Names</i>	<i>Birth and Death</i>	<i>Place of Residence</i>	<i>Meetings</i>
Hall, Henry Martyn, Jr., M.D.	(1872+)	Pittsburgh, Pa.	— — (3)
Halsey, Luther Murphy, M.D.	(1849-1921)	Williamstown, N. J.	— — (3)
Hance, Irwin Howell, M.D.	(1861-1929)	Lakewood, N. J.	— — (3)
Hancker, William Henry, M.D.	(1850-1933)	Farnhurst, Del.	— — (3)
Hare, Hobart Amory, M.D.	(1862-1931)	Philadelphia, Pa.	— (2) —
Hart, James Augustus, M.D.	(1849-1925)	Colorado Springs, Colo.	— — (3)
Hatfield, Charles James, M.D.	(1867+)	Philadelphia, Pa.	— (2) (3)
Hickling, Daniel Percy, M.D.	(1863-1939)	Washington, D. C.	— — (3)
Hinsdale, Guy, M.D.	(1858+)	Hot Springs, Va.	— — (3)
Hirschfelder, Joseph Oakland, M.D.	(1854-1920)	San Francisco, Calif.	— — (3)
Hitchcock, Harry Eastman, M.D.	(1872-1936)	Auburn, Me.	— — (3)
Hoffman, Frederick Ludwig	(1865+)	Newark, N. J.	— — (3)
Holmes, Anderson Mansfield, M.D.	(1862-n.d.)	Denver, Colo.	— — (3)
Holton, Henry Dwight, M.D.	(1838-1917)	Brattleboro, Vt.	— (2) (3)
Hubbard, Thomas, M.D.	(1859-1943)	Toledo, Ohio	— — (3)
Huber, John Bessner, M.D.	(1864-1924)	New York, N. Y.	(1) — (3)
Huddleston, John Henry, M.D.	(1864-1915)	New York, N. Y.	— — (3)
Hurty, John Newell, M.D.	(1852-1925)	Indianapolis, Ind.	(1) — (3)
Ingals, Ephraim Fletcher, M.D.	(1848-1918)	Chicago, Ill.	— — (3)
Irwin, James Willoughby, M.D.	(1871-1921)	Philadelphia, Pa.	— — (3)
Jacobi, Abraham, M.D.	(1830-1919)	New York, N. Y.	— (2) (3)
Jacobs, Henry Barton, M.D.	(1858-1939)	Baltimore, Md.	(1) (2) (3)
Janeway, Edward Gamaliel, M.D.	(1841-1911)	New York, N. Y.	— (2) (3)
Jarrett, Harry S., M.D.	(1861-1919)	Towson, Md.	— — (3)
Kean, Jefferson Randolph, M.D.	(1860+)	Washington, D. C.	— — (3)
Kennaday, Paul	(1873-1929)	New York, N. Y.	(1) — —
King, Herbert Maxon, M.D.	(1864-1917)	Liberty, N. Y.	— (2) (3)
Kinyoun, Maj. Joseph James, M.D.	(1860-1919)	Glenolden, Pa.	(1) — (3)
Kipp, Charles John, M.D.	(1838-1911)	Newark, N. J.	— — (3)
Klebs, Arnold Carl, M.D.	(1870-1943)	Chicago, Ill.	(1) — (3)
Knight, Frederick Irving, M.D.	(1841-1909)	Boston, Mass.	— — (3)
Knopf, Sigard Adolphus, M.D.	(1857-1940)	New York, N. Y.	(1) (2) (3)
Knox, James Hall Mason, Jr., M.D.	(1872+)	Baltimore, Md.	(1) — (3)
Kober, George Martin, M.D.	(1850-1931)	Washington, D. C.	— — (3)
Lambert, Alexander, M.D.	(1861-1939)	New York, N. Y.	— (2) (3)
Landis, Henry Robert Murray, M.D.	(1872-1937)	Philadelphia, Pa.	— (2) (3)
Lewis, Charles M.	(no inf.)	Philadelphia, Pa.	— (2) —
Lewis, Daniel, M.D.	(1846-1919)	New York, N. Y.	(1) (2) —
Lewis, Harry Edwin, M.D.	(1875-1927)	Burlington, Vt.	— — (3)
Linthicum, George Milton, M.D.	(1870-1935)	Baltimore, Md.	— — (3)
Loomis, Henry Patterson, M.D.	(1859-1907)	New York, N.Y.	— — (3)
Lowman, John Henry, M.D.	(1849-1919)	Cleveland, Ohio	— — (3)
Luce, Frank Henry, M.D.	(1859-1937)	Davenport, Wash.	— — (3)
Lyle, Benjamin Franklin, M.D.	(1861-1939)	Cincinnati, Ohio	— — (3)
Lyman, David Russell, M.D.	(1876+)	Wallingford, Conn.	(1) — (3)
McCarthy, Daniel Joseph, M.D.	(1874+)	Philadelphia, Pa.	— (2) (3)
McGahan, Charles Fourgeaud, M.D.	(1861-1910)	Aiken, S. C.	— — (3)
Maher, Stephen John, M.D.	(1860-1939)	New Haven, Conn.	— — (3)
Marcley, Walter John, M.D.	(1867+)	Rutland, Mass.	(1) — —
Marshall, Harry Taylor, M.D.	(1875-1929)	Baltimore, Md.	(1) — —
Meyer, Alfred, M.D.	(1854+)	New York, N. Y.	— — (3)
Middleton, William John, M.D.	(1858-1937)	Steelton, Pa.	— — (3)

FOUNDERS OF THE NATIONAL TUBERCULOSIS ASSOCIATION—*Continued*

<i>Names</i>	<i>Birth and Death</i>	<i>Place of Residence</i>	<i>Meetings</i>
Miller, James Alexander, M.D.	(1874+)	New York, N. Y.	— (2) —
Miner, Charles Howard, M.D.	(1868+)	Wilkes-Barre, Pa.	— (2) —
Minor, Charles Launcelot, M.D.	(1865-1928)	Asheville, N. C.	(1) (2) (3)
Musser, John Herr, M.D.	(1856-1912)	Philadelphia, Pa.	— (2) (3)
Neale, Henry Marion, M.D.	(1858-1937)	Upper Lehigh, Pa.	— — (3)
Newcomb, James Edward, M.D.	(1857-1912)	New York, N. Y.	— — (3)
Nichols, Estes, M.D.	(1874-1944)	Augusta, Me.	— (2) (3)
Norris, George William, M.D.	(1875+)	Philadelphia, Pa.	— (2) (3)
Oertel, Theodore Eugene, M.D.	(1864-1933)	Augusta, Ga.	(1) — —
Osborne, Oliver Thomas, M.D.	(1862-1940)	New Haven, Conn.	— — (3)
Osler, William, M.D.	(1849-1919)	Baltimore, Md.	(1) (2) (3)
Otis, Edward Osgood, M.D.	(1848-1933)	Boston, Mass.	(1) — (3)
Overlock, Melvin George, M.D.	(1865-1920)	Worcester, Mass.	(1) — (3)
Page, Calvin Gates, M.D.	(1867+)	Boston, Mass.	— — (3)
Pease, Herbert Dodge, M.D.	(1870+)	Albany, N. Y.	(1) — —
Peck, Charles William, M.D.	(1841-1916)	Brandon, Vt.	— — (3)
Perkins, Jay, M.D.	(1864+)	Providence, R. I.	— (2) (3)
Peters, William Harlan, M.D.	(1868-1931)	Providence, R. I.	— — (3)
Pettit, James Wiley, M.D.	(1846-1926)	Ottawa, Ill.	— — (3)
Phillips, William Fowke	(1863-1935)	Washington, D. C.	— — (3)
Ravenel, M.D.			
Porter, William Henry, M.D.	(1853-1933)	St. Louis, Mo.	— — (3)
Price, Marshall Langton, M.D.	(1878-1915)	Baltimore, Md.	(1) — —
Probst, Charles Oliver, M.D.	(1857-1933)	Columbus, Ohio	— (2) (3)
Pryor, John Henry, M.D.	(1859-1923)	Buffalo, N. Y.	— (2) (3)
Pulley, William Joseph, M.D.	(1869+)	New York, N. Y.	— — (3)
Putnam, Helen Cordelia, M.D.	(1857+)	Providence, R. I.	— — (3)
Ravenel, Mazýck Porcher, M.D.	(n.d.+)	Philadelphia, Pa.	— (2) —
Reynolds, Walter Seymour, M.D.	(1864-1919)	Atlantic City, N. J.	— — (3)
Richer, Arthur Joseph, M.D.	(1868-1922)	Montreal, Canada	(1) — —
Rochester, DeLancey, M.D.	(1859-1929)	Buffalo, N. Y.	— (2) (3)
Rosenau, Milton Joseph, M.D.	(1869+)	Washington, D. C.	— (2) (3)
Rothrock, Joseph Trimble, M.D.	(1839-1922)	Mt. Alto, Pa.	— (2) (3)
Ruhräh, John, M.D.	(1872-1935)	Baltimore, Md.	(1) — (3)
Schauffler, William Gray, M.D.	(1863-1933)	Lakewood, N. J.	— — (3)
Schmitt, Gustav, M.D.	(1862+)	Milwaukee, Wis.	— — (3)
Sewall, Henry, M.D.	(1855-1936)	Denver, Colo.	— — (3)
Simmons, George Henry, M.D.	(1852-1937)	Chicago, Ill.	— — (3)
Solis-Cohen, Solomon, M.D.	(1857+)	Philadelphia, Pa.	— (2) (3)
Solly, Samuel Edwin, M.D.	(1845-1906)	Colorado Springs, Colo.	— — (3)
Stanton, William Bancroft, M.D.	(1872-1910)	Philadelphia, Pa.	— (2) (3)
Sternberg, Brig. Gen. George	(1838-1915)	Washington, D. C.	— (2) (3)
Miller, M.D.			
Stevens, Martin Luther, M.D.	(1864-1940)	Asheville, N. C.	— — (3)
Stockdale, Rev. Elwell	(1873-1917)	White Haven, Pa.	— (2) (3)
Stockton, Charles Gleason, M.D.	(1853-1931)	Buffalo, N. Y.	— — (3)
Stokes, William Royal, M.D.	(1870-1930)	Baltimore, Md.	— — (3)
Stone, Arthur Kingsbury, M.D.	(1861+)	Boston, Mass.	— (2) —
Stubbert, James Edward, M.D.	(1859-1938)	New York, N. Y.	— (2) (3)
Swain, Henry Lawrence, M.D.	(1864-1940)	New Haven, Conn.	— — (3)
Swarts, Gardner Taber, M.D.	(1857-1925)	Providence, R. I.	— — (3)

FOUNDERS OF THE NATIONAL TUBERCULOSIS ASSOCIATION—*Continued*

<i>Names</i>	<i>Birth and Death</i>	<i>Place of Residence</i>	<i>Meetings</i>
Taylor, Henry Longstreet, M.D.	(1857-1932)	St. Paul, Minn.	— — (3)
Taylor, John Martin, M.D.	(1861+)	Boise, Idaho	— (2) —
Thayer, William Sydney, M.D.	(1864-1932)	Baltimore, Md.	(1) — —
Trudeau, Edward Livingston, M.D.	(1848-1915)	Saranac Lake, N. Y.	— — (3)
Turnbull, Thomas, Jr., M.D.	(1865+)	Allegheny, Pa.	— — (3)
Tyson, James, M.D.	(1841-1919)	Philadelphia, Pa.	— (2) (3)
Tyson, Thomas Mellor, M.D.	(1866-1928)	Philadelphia, Pa.	— (2) (3)
Ullom, Josephus Tucker, M.D.	(1877+)	Philadelphia, Pa.	— (2) —
Vaughan, Victor Clarence, M.D.	(1851-1929)	Ann Arbor, Mich.	— — (3)
Vietor, Agnes Caecilia, M.D.	(n.d.+)	Boston, Mass.	— (2) (3)
Von Ruck, Karl, M.D.	(1849-1922)	Asheville, N. C.	— — (3)
Wainwright, Jonathan Mayhew, M.D.	(1874-1934)	Scranton, Pa.	— — (3)
Walker, Samuel Johnson, M.D.	(1867-1924)	Chicago, Ill.	— — (3)
Walsh, Joseph, M.D.	(1870+)	Philadelphia, Pa.	— (2) (3)
Ward, Samuel Baldwin, M.D.	(1842-1915)	Albany, N. Y.	— (2) —
Welch, William Henry, M.D.	(1850-1934)	Baltimore, Md.	(1) (2) (3)
Wells, Edward Franklin, M.D.	(1853-1925)	Chicago, Ill.	— — (3)
White, William Rushmer, M.D.	(1875-1939)	Providence, R. I.	— — (3)
Wilder, John Archibald, M.D.	(1870-1911)	Denver, Colo.	— — (3)
Willcox, James Mark	(1861-1935)	Philadelphia, Pa.	— (2) —
Williams, Francis Henry, M.D.	(1852-1936)	Boston, Mass.	— (2) —
Willson, Robert Newton, M.D.	(1873-1916)	Philadelphia, Pa.	— — (3)
Wilson, Gordon, M.D.	(1876-1932)	Baltimore, Md.	— — (3)
Wilson, James Cornelius, M.D.	(1847-1934)	Philadelphia, Pa.	— (2) (3)
Young, William Archibald, M.D.	(1866-1933)	Toronto, Canada	(1) — —

Explanation: Final authority for spelling and dates has been the files of The Journal of the American Medical Association or the current issue of The Directory of the American Medical Association. Symbols used: + = continuous to date; n.d. = no date given; no inf. = no information. Meetings attended indicated by (1) = Baltimore; (2) = Philadelphia; (3) = Atlantic City.

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Tuberculosis in Industry

Dr. Leroy U. Gardner, *Chairman*

Dr. Leopold Brahdy

Dr. Oscar A. Sander

Dr. Lloyd Hamlin

*Mr. B. E. Kuechle

Dr. Herman E. Hilleboe

*Dr. William P. Shepard

Dr. Ada Chree Reid

*Dr. C. D. Selby

*Mr. William A. Doppler

The Committee on Tuberculosis in Industry, a joint committee of the National Tuberculosis Association and the American Trudeau Society, held its annual meeting in Pittsburgh, Pennsylvania on November 15, 1944.

Fair Employment Standards: The Subcommittee appointed at the November meeting has in preparation a guide for industrial physicians, setting standards on the industrial employability of persons with a history of tuberculosis.

A. M. A. Cooperation: The Committee is collaborating with the Council on Industrial Health of the American Medical Association in codifying industrial case-finding procedures.

Industrial X-ray Atlas: Dr. Leroy U. Gardner has accepted the Committee's invitation to prepare a collection of chest X-ray plates of industrial significance for publication by the National Tuberculosis Association.

NTA-ATS Symposium, "Tuberculosis and Silicosis": The symposium on tuberculosis and silicosis, authorized by the Committee at its November meeting, is in the hands of the printer and should be available in the fall of 1945.

Industrial Mass Radiography Manual: Doctor Hilleboe's volume on mass radiography of the chest is now on the market. This book eliminates the immediate need for a Committee publication on the same subject, such as was recommended by the 1944 Committee.

* National Tuberculosis Association Members.

AMERICAN TRUDEAU SOCIETY

Report of the Committee on X-ray Apparatus and Technique

Dr. Wm. H. Weidman, *Chairman*

Dr. Ezra Bridge

Dr. Hollis Potter

Dr. F. Maurice McPhedran

*Mr. Edward F. Gunson

Dr. Russell H. Morgan

*Dr. S. Reid Warren

A meeting of the Committee on X-ray Apparatus and Technique was held on December 1, 1944. Committee members present were: Wm. H. Weidman, M.D., Chairman, Ezra Bridge, M.D., Russell H. Morgan, M.D., F. Maurice McPhedran, M.D., S. Reid Warren, D.Sc., Edward F. Gunson.

Because of the development of unforeseen circumstances, Dr. Hollis Potter was unable to attend. Dr. R. S. Gass of Tennessee, having been given an overseas assignment by the U. N. R. R. A. requested that the Committee accept his resignation. This was done with regret.

Physical Factors Affecting Diagnostic Quality of Radiographic Films: Doctor Morgan reported that the interpretability of a radiographic film is governed by certain subjective factors related to the radiologist who reads the film and by certain physical factors related to the clarity with which the radiographic group, however, is amenable to analysis by usual physical methods.

The clarity of the radiographic image is dependent on certain related factors. These include: (1) the maximum ability of the radiographic film to record detail, (2) the inherent contrast coefficient of the radiographic material, (3) the contrast of the roentgen image and its surrounding field, (4) unsharpness of the image as introduced by movement of the structures being radiographed or by the finite size of the target, (5) certain physiological limitations of the viewer's eye.

Each of these subdivisions has been investigated for various kinds of radiographic films, screens, photofluorographic materials and for various radiographic techniques through a wide range of kilovoltage, and through a wide range of tissue thickness; both for calcified and soft tissues, and both for Potter grid and non-grid radiography. From these data it is possible to present in unequivocal terms the value of one radiographic material over another, and the value of one technique over another. (These data are to be published in detail later.)

Reproduction of Chest Roentgenograms on Paper: Samples of reproduction were submitted by Dr. Bridge and Mr. Warren and those submitted by Mr. Warren were considered to be acceptable by the Committee. In order to facilitate the development of this project, it was decided that a Subcommittee be formed consisting of Dr. Bridge, Mr. Warren and Dr. Morgan. This Committee is to work out all details and is to complete this project before the next

* National Tuberculosis Association Members.

scheduled meeting of the American Trudeau Society. It is to be understood that the reproductions are to be printed on paper having an overall size of $8\frac{1}{2}$ " x 11". Most of the Committee members felt that an acceptable format for these paper reproductions should be of the loose-leaf folder type so that, if this project meets with general approval, additions could be made from time to time. As time passes, an X-ray manual could be obtained. It is hoped that these reproductions will be distributed without cost to the individual members of the Society. It was decided to make arrangements with the National Tuberculosis Association for the distribution of paper copies of three of the technique films. One film illustrating underexposure, one regular technique and one overexposure.

X-ray Film Library: Doctor Weidman, with the help of Mr. Jean Kieffer, submitted a group of X-ray films demonstrating various technical factors arranged in a booklet form to be used for general distribution among the members. However, because of technical difficulties, it was decided to temporarily hold this project in abeyance.

Body Section Roentgenography: Doctor McPhedran reported further developments on his investigation of planigraphy. The problem of the appearance of the lesion on different planes at greater depths than the size of lesion warrants was discussed. He is to continue his work and submit a report at a later date. Doctor McPhedran also demonstrated the value of frequent serial roentgenograms taken at short intervals of time. By using lead filters many exposures could be obtained on the ordinary 14" x 17" film.

American Society of X-ray Technicians: Mr. Gunson will attempt during the coming year to further develop the close relationship and coöperation between this Society and that which he represents in order to improve, if possible, X-ray technique. It was suggested that possibly the Society of X-ray Technicians might increase its membership through the American Trudeau Society by canvassing the various sanatoria employing X-ray technicians, and this list will be made available to the National Tuberculosis Association office.

Stereoscopy: Doctor Bridge suggested that knowledge on this subject is far from complete and at the next meeting Mr. Henry Kurtz, who is an expert on stereoscopy, will present certain problems for discussion and investigation.

NOTICE

Conference on Tuberculosis

A Conference on Control of Tuberculosis in a Metropolitan Area, sponsored by the Institute of Medicine of Chicago, will be held on Tuesday and Wednesday, November 13 and 14, 1945, at the Palmer House, Chicago, and will cover phases that are of particular importance at this time to clinicians, specialists, lay workers, and teachers, who are cordially invited to attend. Among the subjects to be discussed by local and national authorities in the field of tuberculosis and public health are the following:

Application of Immunological Principles to the Clinic of Tuberculosis

Case Finding

Tuberculosis in Negroes

Dietary Aspects of Tuberculosis

Climatic Aspects of Tuberculosis

Sanatorium Facilities

The Rôle of General Hospitals and Clinics and of the Private Physician in Tuberculosis

Tuberculosis and Housing

The Family Problem of the Tuberculous Patient

Education of Public Authorities and the Laity in Tuberculosis

Tuberculosis in Children; Tuberculosis as a School Problem; The Practical Application of Instruction Methods for Schools

Principles and Organization of Treatment

Surgical Treatment of Tuberculosis

Follow-up Problems, Including the Chronic Open Case

Rehabilitation

The Rôle of Governmental Agencies

Panel Discussions

Financing the Tuberculosis Problem

The Problem of the Tuberculous War Veteran

Immunization with the Bacillus Calmette-Guerin

Education of Medical Students and Physicians in Tuberculosis

For further information and programs, address: The Institute of Medicine of Chicago, 86 East Randolph Street, Chicago 1, Illinois.

THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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ABST. No. 4

Hemoglobin at High Altitudes.—The position of the oxygen dissociation curve has been determined in arterial blood obtained from (a) 17 healthy adult men living at sea level; (b) 12 Indian native residents of Morococha (Peru), at an altitude of 4,540 meters (14,890 ft.). The same determination has been repeated in 12 subjects of the first group within the first two hours after arrival at the high altitude, and in 8 men of the second group also within the first two hours after arrival at sea level. The results have been compared with those obtained in previous investigations. There seems to be enough evidence to conclude that in humans, new-comers or residents, at altitudes of about 4,000 meters or higher, there is no increased affinity of the blood hemoglobin for oxygen. On the contrary, the findings indicate a slight tendency toward a lower affinity, both at arterial pH and a standard pH of 7.40, especially in the native residents. This right shift in the oxygen dissociation curve at high altitudes may be interpreted as a favorable compensatory adjustment to the low pressure environment. (Authors' summary.)—*The Affinity of Haemoglobin for Oxygen at Sea Level and at High Altitudes*, H. Aste-Salazar & A. Hurtado, *Am. J. Physiol.*, December, 1944, 142: 733.—(G. C. Leiner)

Pulmonary Syphilis.—This is a detailed review on pulmonary syphilis from a pathological point of view, based on the observation of a series of lungs with acquired or congenital syphilitic lesions. The division of syphilis into three periods is compared with the known scheme of Ranke concerning tuberculosis.

The division in the case of syphilis is not based on an immunological conception and the lesions in tertiary syphilis have a definite pattern, while in the tertiary tuberculous lesions an anatomic polymorphism prevails; besides these differences, the division in the case of syphilis responds to practical needs and is adequate, while Ranke's scheme, although the best attempt as yet made to obtain a global vision of tuberculosis, is still widely debated and insufficient for practical use. The microscopic examination of syphilitic specimens has two objectives: the demonstration of the treponema in the fresh material with the usual techniques and the histological study of the tissue changes. For the latter, the fixation of the lung by 10 per cent formol solution, before the opening of the chest, is advised. Postmortem X-ray examination is also a useful technique. The participation of the bronchi in form of gummosis bronchitis or bronchiolitis obliterans was evident in all cases. Peribronchial lesions were also present. The possible rôle of syphilis in the genesis of bronchiectasis and also the possible relationship between congenital cystic lung disease and syphilis are pointed out. The part played by the parenchyma in pulmonary syphilis is not clear. Nodular alveolar lesions were seen only exceptionally; more often bronchopneumonic alterations were found, either of the nonspecific type, with cellular and aluminous exudate of the acute type, or specific infiltration with mononuclear cells. The alveolitis was mostly accompanied by interstitial pneumonia. The interstitial tissue is the site of the most important and extensive

alterations. Vascular lesions of all layers and types were found in the material. Among the sequelae of the syphilitic process, cavities are rare; more frequent is sclerosis of different types, from simple linear sclerosis to extensive indurative syphilis. Various changes can be found around syphilitic lesions, such as edema, congestion, interstitial hemorrhages, pigment deposits, emphysema, atelectasis, carnification. In 2 cases exudative pleurisy was found, without any character of specificity. The gross anatomic appearance of pulmonary syphilis is rarely that of a single syphilitic gumma. Diffuse or modular gummata are frequent in the pneumonic or bronchopneumonic type of lesions. When the gross appearance of the lesions is that of sclerosis, only the presence of micro-gummata can confirm the diagnosis. Sometimes suppuration or gangrena complicates the picture. There is no agreement about the mutual influence of coexistent syphilis and tuberculosis, and the limited number of observations in this review brings no conclusive evidence in either sense. Congenital pulmonary syphilis is characterized by the abundance of treponemata that are easily demonstrated. The gross anatomic appearance is that of the so-called "pneumonia alba." In the microscopic picture there are alveolar infiltration, interstitial lesions and a pseudoglandular aspect of the lung, corresponding to the early phase in the embryonal development of the lung. This thorough study proves once more the difficulty of the anatomopathological diagnosis of pulmonary syphilis and it emphasizes the diagnostic value of the demonstration of the treponema in questionable specimens.—*Las sífilis pulmonar*, A. L. Matteo, *Arch. tisiol. y pneumol.*, 1943, 2: 209.—(L. Molnar)

Pulmonary Syphilis.—A syphilitic process of the lungs and airways can be easily mistaken for tuberculosis, bronchopulmonary gangrene, neoplasm, mycosis or bronchiectasis. Repeated attacks of "influenza" or pneumonia, as well as signs of diminished aeration of the lungs should always lead to a suspicion of syphilis. The most frequent location of pul-

monary syphilis is in the left lower lobe. The authors present a case that had been diagnosed and treated for many months as a primary neoplasm of the lungs. When this patient was first seen he presented an almost complete aphonia and a tracheo-cutaneous fistula was found in the region of the cricoid cartilage, which was completely destroyed. The serological examinations were always negative and only after a diagnostic injection of arsphenamine did the Wassermann test turn positive. The symptoms subsided on specific antiluetic treatment.—*Sífiloma pulmonar con localización laringea*, J. M. Remolar, V. Thompson & G. Caputo, *Rev. Asoc. méd. argent.*, May 30, 1944, 58: 340.—(W. Swienty)

Pulmonary Mycosis.—This article is intended as a review and summary of the literature regarding yeast infections of man, especially of the lungs. It is believed that, from a practical standpoint, there is sufficient similarity in the lesions produced that all yeast infections may be discussed as a single entity, any variation being chiefly one of degree of virulence. Practically no regions are exempt, though some have a higher incidence, such as coccidioidomycosis in the San Joaquin Valley. Susceptibility varies little with race, color or age, but depends mostly upon geographical location. Neither does there seem to be any occupational prevalence. In spite of the frequent number of cases of blastomycosis of the skin encountered among persons raising or handling cattle, the incidence of pulmonary mycosis is no higher than in any other occupation, though by contrast a newcomer to the San Joaquin Valley may contract a mycotic infection while the natives have little trouble. The spores of yeast are very resistant to heat, cold and drying, but grow in a slightly acid medium. Since the body fluids are slightly alkaline, it is possible that some other disease may temporarily change the pH so that organisms may begin to grow. Primary infection occurs most frequently through the respiratory tract, possibly bronchial ulceration, allowing the yeast to gain a foothold. Yeasts do not seem to produce much defense

mechanism by the body. Extension may occur from the yeast alone, in conjunction with some infection, or areas of bronchopneumonia may develop as the result of an associated disease taking advantage of the injury done by the yeast. At some stage in the spread, a large number of organisms must get into the blood or lymph stream of the more virulent infections producing new areas of infection all through the body which grow rapidly and are of high degree of toxicity, especially in coccidioid and torula infections. Probably most yeast infections never get beyond the bronchi. Microscopically the lesion of a mycotic infection is a tubercle-like granuloma. Complicated by other infections, it will also show the microscopic cell structure of these infections. The symptoms of pulmonary mycosis vary in degree and type depending upon the virulence of the infection, extent and rapidity of extension. In mild cases the symptoms are those of any pulmonary infection, a chronic cough, often productive, being the most common symptom. In severe cases there may be fever, hemoptysis and other evidence of pulmonary disease, a foul nauseating sputum being the only sign suggestive of a fungus infection. In disseminating disease, the symptoms depend on the organ involved. Physical examination often reveals few abnormal findings, and these are present also in tuberculosis and other pulmonary diseases. In some cases the physical findings are extensive, but often they do not indicate any severe changes, and the clinician may be surprised at the extensive disease shown by the X-ray film. While the clinician is the first to recognize the pulmonary disease, the roentgenologist can often suggest its nature, and the pathologist or bacteriologist must make the final diagnosis by actual demonstration of the fungus itself. Probably the earliest roentgen findings are only increased marking of the bronchovascular tree and some irregular peribronchial infiltration which may be unilateral. No enlargement of the lymph nodes was found in any of the cases studied. Later patchy areas of density appear in the parenchyma, miliary in size or as large nodules, which may

increase, coalesce and break down into abscesses. The lesions may gradually extend toward the periphery, eventually producing pleural thickening. Another type of involvement may show faint, fuzzy shadows along the bronchovascular tree giving a ground glass appearance. Advanced cases may present discrete nodules in the pulmonary parenchyma quite dense and not sharply demarcated, varying in size, isolated or conglomerate. During convalescence these lesions may melt away like snow, and extensive changes take place in a few weeks as compared to the slow change seen in tuberculosis. Some do not clear entirely but leave areas of fibrosis and chronic cavities. Tuberculosis frequently does develop in a mycotic lung, and it would be difficult to tell which disease occurred first. The tendency to attach little significance to the presence of yeast once a tubercle bacillus is demonstrated may be a definite mistake for the yeast may play an active part in the lung, and little improvement may be expected until the fungus infection is largely eradicated. X-ray differentiation from tuberculosis is not at all reliable. Other diseases from which mycotic infection must be differentiated are sarcoidosis, cancer metastases, bronchopneumonia, atypical and virus pneumonia and the nodular stage of pneumoconiosis. The most widely used and successful treatment appears to be the use of iodides and X-ray. Increasing doses of potassium iodide by mouth and sodium iodide intravenously, even in the presence of tuberculosis, and X-ray radiation once or twice a week over the chest and skin lesions, using not over 100 r per area treated, are used. Some authors believe that the patient must be desensitized to the yeast before receiving iodides in the treatment of moniliasis and blastomycosis. Lucas vaccine 0.1 cc. twice daily increasing to 0.8 cc. or immune rabbit serum may be used. Cases are reported demonstrating some of the difficulties encountered in evaluating the importance of yeast in the sputum, where there may be a pure infection, a secondary infection which assumes a primary rôle in the extension of the original disease, the secondary disease or both.

The authors feel that yeast infections are more prevalent than ordinarily thought.—*Clinical and Radiological Studies of Pulmonary Mycosis*, W. A. Johnston & J. Heydemann, *Radiology*, July, 1944, 43: 1.—(G. F. Mitchell)

Fungus Diseases of Chest.—A group of proved cases of infection of the lungs due to fungus infection are presented. In approximately one-fourth of these cases, there were fungus infections elsewhere in the body. Such extrapulmonary lesions are an aid in the differential diagnosis of the pulmonary lesion. Twenty-four cases of coccidioidomycosis were diagnosed by sputum culture, positive skin tests or blood agglutination tests. The X-ray evidence of these cases varied greatly. The most frequent lesion was a solitary nodose area of infiltration that later broke down leaving a thin-walled cavity, but at times the nodose lesions were scattered throughout the lung so that they gave the appearance of metastatic carcinoma. In other cases they closely resembled tuberculous lesions involving one or both apices or midlung field. About half of the patients showed slight enlargement of the hilar lymph nodes. During the time of observation, the infiltrative lesions cleared slowly with only slight change in the size of the cavities. The histories were indefinite, but all were from southwestern United States. In most there was little clinical evidence of disease at the time of admission to the hospital. The residual cyst-like cavities reported by Winn and Johnson were demonstrated in these cases, and while no lipiodol studies were made, a number would undoubtedly also show bronchiectasis. One patient had a positive coccidioidin skin test and negative tuberculin test, and while there was no history of infection, it is assumed that the parenchymal scar was due to coccidioidomycosis. In actinomycosis there is an early extension from the lung into the pleura, and the latter involvement may obscure the underlying pulmonary lesions. Nine of the cases observed showed early or late pleural involvement. The lungs showed infiltration which could not be differentiated from tuberculosis; one or both lungs were in-

volved and abscess formation usually was early and often obscured by the pleural lesions. Cases coming to autopsy revealed extensive pleural and pulmonary involvement usually extending through the diaphragm to the abdominal viscera. In the group of cases classified as aspergillus infections, similar radiographic finds were present, X-ray films revealing a soft, irregular, peribronchial or parenchymal infiltration and often enlargement of the hilar lymph nodes. All showed rapid clearing with iodide therapy, and one cleared without therapy on bed-rest. In such cases, if repeated sputum tests for tubercle bacilli are negative, one may be justified in suggesting iodide therapy and basing the diagnosis on the response to treatment. The author reports examining roentgenograms in which multiple irregular areas of calcification are seen in the parenchyma and hilar nodes with or without a negative tuberculin test. This type of calcification is regarded as the residual of a healed fungus infection. *Monilia albicans* is commonly harbored by man and, while it frequently is a secondary invader in pulmonary disease, it may also produce primary pulmonary lesions. As seen on X-ray films there is a diffuse bilateral and fairly symmetrical, peribronchial infiltration. One case broke down with resultant cavity formation. If treated the lesion resolves rapidly with residual fibrosis. Torulosis and blastomycosis are rare in man and usually produce parenchymal lesions similar to those seen in tuberculosis. One case observed over a period of six years and diagnosed as tuberculosis despite repeated negative sputum tests died of a miliary spread and was found at autopsy to have blastomycosis. Thus, while fungus infections of the lung are not common, they do occur, and it is important that an early diagnosis be made before extensive damage occurs as many of the lesions will respond to therapy. A wide variety of lesions as seen roentgenologically may be found, but if familiar to the radiologist much help may be given in the diagnosis. Final diagnosis rests upon isolation of the fungus as well as absence of other etiological factors. The lesions most

often resemble a tuberculous involvement. Therefore, any lesion having the appearance of tuberculosis in which no tubercle bacilli can be found should be studied carefully to rule out a fungus infection, and where no definite organism can be isolated a therapeutic test with iodides may be instituted, and the final diagnosis based upon the response. It is possible that many of us will be seeing cases of fungus infection due to coccidioides as men are returned from army camps, and it is important that the true nature of the lesion be recognized.—*Fungus Disease of the Chest*, V. L. Peterson, *Radiology*, July, 1944, 43: 14.—(G. F. Mitchell)

Coccidioidomycosis.—Fourteen patients with proved diagnosis of coccidioidomycosis and 30 patients in whom the diagnosis was suspected but not confirmed were observed. Of the 14 patients, 10 had primary benign and 4 had progressive disseminated coccidioidomycosis. The history of exposure in an area where the disease is endemic is of importance for the diagnosis. All patients had been in such areas. In 4 patients the onset was with the clinical picture of pneumonia, in 2 like pneumonia with pleural effusion, in 5 insidious with cough, weakness and slight fever, in 3 the disease was discovered by repeated routine cutaneous tests. Usual symptoms were cough, pain in the chest; however, there are no symptoms or signs pathognomonic of primary chronic coccidioidal infection. Reaction to intracutaneous injection of coccidioidin, in dilutions of 1:1000 and 1:100, probably indicates that the patient has or has had at some time in the past a coccidioidal infection. A negative coccidioidin reaction generally excludes coccidioidomycosis; but disseminated coccidioidomycosis may have a negative phase. Examination by direct smear is not reliable; culture and inoculation into a guinea pig or mouse should always be done. Serological tests are of help for establishing the diagnosis; negative serological tests speak against the diagnosis of disseminated coccidioidomycosis, but not against primary infection. Sometimes it is advisable to make

cultures from material obtained by biopsy. X-ray findings may be simple hilar thickenings, pneumonic infiltrations, massive effusions; solitary, thin-walled cavities with little surrounding reaction are characteristic. Treatment is symptomatic. For the pulmonary lesions bed-rest is advised. Immobilization of the lung by a lead shot bag on the chest seemed to be of benefit. Phrenicotomy was done in 2 cases with good effect. Chemotherapy is of no value.—*Diagnosis and Treatment of Chronic Coccidioidomycosis*, E. J. Denenhöf & G. Cheney, *Arch. Ind. Med.*, November, 1944, 74: 811.—(G. C. Leiner)

Coccidioidomycosis.—Pulmonary lesions in 75 cases of primary coccidioidomycosis were studied. The clinical symptoms of the disease consist of dry cough, chest pain, malaise, fever, weight loss and night sweats. As a rule, recovery occurs in two to six weeks; rarely, disseminated granulomatosis develops and, then, the outcome is fatal. Recent exposure to dust containing the chlamydospores of the fungus, no history of previous exposure, a certain incubation period, positive intracutaneous coccidioidin reaction and positive complement fixation were the required diagnostic criteria in the cases studied. Twenty-four per cent of the cases exhibited increased hilar densities only, representing subacute inflammatory changes in the mucosa and submucosa of the larger bronchi and in the lymphatics. In some of these cases circumscribed lymphadenopathic shadows were seen; the latter are probably explained by more marked involvement of lymphatic structures. In 38.7 per cent of the cases fan-shaped densities were seen extending from the hilum outward, and these persisted for 15 to 90 days; pathologically, they signify involvement of the tertiary bronchi and bronchioles, together with proliferative and cellular peribronchial infiltration. Lobular and sublobular exudates, representing further extension into the pulmonary parenchyma, were found in 26.6 per cent; resolution was slow, averaging 37 days. In 3 cases (4 per cent) there was cavitation, lasting 60 days in one case, 95

days in the other, and persisting in the form of a thin walled cyst in the third. In one case intermittent ballooning of the cavity was observed. Two cases (2.7 per cent) had massive pleural effusion which resulted in considerable pleural thickening. Slight to moderate pleuritis was seen in 7 other cases. Among the above roentgenological types increase in the hilar shadow was the most constant finding. Delayed but complete resolution is considered characteristic of the disease.—*Roentgenological Types of Pulmonary Lesions in Primary Coccidioidomycosis*, J. R. Colburn, *Am. J. Roentgenol.*, January, 1944, 51: 1.—(P. Lowy)

Blastomycosis of Lung.—Ayerza coined the expression, "Cardiaco Negro," for a syndrome of cardiac insufficiency and severe impairment of the pulmonary circulation which causes typical deep black cyanosis. Various etiological factors may contribute to cause this syndrome. A case with unusual etiology is presented. The patient who entered the hospital in the terminal stage of the disease presented an extensive cyanosis, severe dyspnea, edema, clubbing of fingers and an emphysematous thorax. The heart sounds were normal but for an accentuation of the second pulmonary sound. Over the base of the lungs some coarse râles were found. In the nasal septum a scar resulting from blastomycotic ulceration was found which he had had for two years and which had healed on administration of sulfathiazole. X-ray examination showed generalized pulmonary fibrosis, especially of the left lower lobe, with pleural effusion and an enlargement of the entire heart, but chiefly of the left side. The autopsy revealed a riding thrombus of the bifurcation of the pulmonary artery, sclerosis of the aorta and numerous nodes with all the morphologic characteristics of blastomycosis throughout the entire lung. Similar lesions were found in the cortex of the adrenal glands. Three principal types of blastomycosis have to be considered: (1) the micoderma or cryptococcus (Gilchrist and Stokes), (2) the coccidioides (Gilchrist and Rixford), (3) the paracoccidioides brasiliensis. From the orig-

inal lesion in nose and septum the lungs and the suprarenals were infected either by the lymphatics or, more probably, by the bloodstream.—*Blastomycose do pulmao e das capsulas suprarrenais: Sindromo de Cardiaco Negro*, A. de Almeida Prado, *Rev. Asoc. méd. argent.*, September 30, 1944, 58: 739.—(W. Swienty)

Actinomycosis.—A case of generalized actinomycosis is reported. The first manifestation was a painful swelling in the left axilla, from this 30 cc. of thick white pus was removed but no organisms were found. Ten days later the axilla was again incised, a biopsy was done, the pus was reexamined and a diagnosis of actinomycosis was made. All modern methods of treatment were employed without appreciably affecting the progress of the disease. Four weeks after admission an enlargement resembling a left inguinal adenitis appeared and one month after admission the presence of pulmonary findings was noted; chest films at this time revealed multiple deposits distributed evenly through the parenchyma of both lungs although a chest film eleven days previously was normal. Death occurred seven weeks after admission; the final pathological picture resembled in many respects the end result in miliary tuberculosis. The finding of inflammatory tissue in the thoracic duct suggests this origin for the hematogenous spread.—*Actinomycosis: Report of a Case with Miliary Chest Lesions*, A. M. Harris & J. B. Priestley, *J. Lab. & Clin. Med.*, August, 1944, 29: 815.—(F. G. Petrik)

Actinomycosis and Diabetes.—Generalized actinomycosis is an infrequent disease in Uruguay. In the past several years only 2 deaths have been reported to the register of vital statistics. The author presents one case report. The patient, a 51 year old male, came under observation because of a lung abscess which resolved completely after sulfonamide and arsenical therapy. Two years later diabetes appeared, controlled at first by diet and later with 20 to 30 units of insulin. Three months later a cold abscess of the dorsal

spine slowly developed, followed by a pulmonary lesion in the left lower lobe, a pleural effusion and chest wall abscess. Actinomyces identified as *Cohnistreptothrix Israeli* were cultured on two occasions from the pus of the chest wall abscess. A week after the first aspiration of pus the patient died. Because of the marked dyspnea and tachycardia the possibility of a mycotic cerebral lesion was considered. There was no autopsy.—*Actinomicosis generalizada de tipo septicopiohemico en enfermo diabetico, R. Rimini, Rev. de tuberc. d. Uruguay, No. 1, 1944, 12: 39.*—(R. Kegel)

Atypical Pneumonia.—The fairly typical clinical course and distinctive X-ray findings have given this relatively new disease a place in its own right. It is a disease of young people with a predilection for males, but any age group may be affected. The onset is with signs and symptoms of an upper respiratory infection. X-ray findings are prominent early and increase for a few days, whereas physical signs in the chest are wanting or negligible. The lower lobes are predominantly affected, and especially the paracardiac region is frequently involved. The sputum shows no predominance of any single organism. Occasionally pneumococci are found which cannot be typed in the majority of cases. The white count is slightly elevated, with a predominance of polymorphonuclears. It may reach as high as 20,000, but this is unusual. Sulfonamide treatment is of no avail. Therapy is entirely symptomatic and must be directed at the distressing cough, and in the severe cases at dyspnea. Complications are few. Sinusitis and bronchiectasis have been encountered. There were 3 fatal cases in a series of 122 in which the disease was definitely diagnosed. Two of the fatal cases were autopsied. They showed patchy areas of bronchopneumonia with purulent bronchitis. The alveoli contained much amorphous pink staining material and large macrophages filled with pigment. No inclusion bodies were found.—*Primary Atypical Pneumonia of Unknown Etiology, S. Gundersen, New Eng-*

land J. Med., November 23, 1944, 231: 697.—(H. Marcus)

Atypical Pneumonia.—Roentgenographic findings in 178 cases of primary atypical pneumonia of unknown etiology are described. Eighty per cent of the lesions were in one of the lower lobes. As a rule, the infiltration is peribronchial; in cases with apparently lobar involvement lateral roentgenograms usually reveal a segmental, confluent bronchopneumonia. In one group of cases the pneumonia manifests itself as a homogeneous, usually slight density, in another the densities are flocculent; occasionally these two types may be coexistent. Of the cases observed 46.4 per cent belonged to the first group, 39.7 per cent to the second and 13.9 per cent to the third. In all three groups the appearance of infiltrations is preceded by a structural accentuation localized to the involved part of the lung. In the homogeneous group beginning resolution is indicated by a decrease in density, giving the lesion a moth-eaten appearance. Pleuritis with effusion is uncommon; lateral views may be necessary to differentiate it from parenchymal infiltrations. Elevation of a hemidiaphragm, interpreted as evidence of atelectasis, was observed in 38 cases. Occasionally Fleischner's lines are present, but other signs of atelectasis are usually absent. In the majority of cases anatomical resolution of infiltrations takes approximately two weeks. Nonresolution was seen in 5 patients, 3 of whom showed clinical, and 2 of the latter roentgenological, evidence of bronchiectasis. The 2 remaining cases had clinical signs of asthma.—*The Roentgenographic Manifestations of Atypical Pneumonia of Unknown Etiology, W. E. Cryslar, Am. J. Roentgenol., March, 1944, 51: 280.*—(P. Lowy)

"Virus" Pneumonia.—Encouraged by the good results of roentgen therapy in the treatment of the severe cough that frequently persists long after the acute stage of "virus" pneumonia has subsided, the author employed radiation treatment in the early phase

of the disease. The following factors were used: 130-150 kv., 30 ma., 0.5 mm. Cu plus 1 mm. A 1 filtration, 50 cm. anode-skin distance, an average dose of 50 r (measured in air), 20 by 20 cm. portals. Fifty-six patients with clinical and roentgenological evidence of "virus" pneumonia were treated, and in 45 of them the results were good. Fever and cough gradually subsided, frequently within sixteen hours following treatment; roentgenological improvement did not run parallel to the clinical course. All patients (18) in whom treatment was instituted within five days of the onset of the disease responded favorably. Of 16 patients who had been ill for over two weeks before treatment was started, only 8 showed improvement. Roentgen therapy of "virus" pneumonia in the early stages of the disease is therefore recommended, with doses not exceeding 100 r.—*Roentgen Therapy of "Virus" Pneumonia*, A. Oppenheimer, *Am. J. Roentgenol.*, May, 1943, 49: 635.—(P. Lowy)

Acute Pneumonitis.—During a four-month period 534 patients were admitted to a Naval Air Station Dispensary with the diagnosis of acute catarrhal fever; 145 of these patients had chest roentgenograms taken and 74 of these showed an area of pulmonary consolidation. The authors review some of the literature of acute pneumonitis (virus pneumonia, acute interstitial pneumonitis, atypical pneumonia or atypical bronchopneumonia of unknown etiology) and present their own findings. The disease is sometimes asymptomatic and is discovered accidentally. Other cases have but mild symptoms of an upper respiratory infection with moderately elevated temperature, and still others run high fever for several days; a second rise of temperature may also occur. A dry or slightly productive cough of varying severity is usually present. Physical signs over the chest may be entirely absent or inconclusive; sometimes, however, coarse râles persist after apparent recovery. The prognosis is generally good. Roentgenologically, the consolidation is most frequent in the lower and middle lobes, than in the hilar region, and is at least common in the upper lobes. At

first a poorly defined hazy density is seen, which later becomes denser and then patchy. The area of consolidation is usually out of proportion to the paucity of clinical symptoms. The leucocyte count is normal or slightly elevated, occasionally diminished. The etiology is unknown; a virus is suspected by most investigators. At autopsy the principal findings are hemorrhage and edema. Mononuclear cells predominate in the exudate, fibrin is absent. Treatment is symptomatic; chemotherapy is ineffective and should be avoided. The authors present 7 illustrative cases and emphasize the frequency and communicability of the disease.—*Acute Pneumonitis*, W. G. Scott & H. L. Jones, Jr., *Am. J. Roentgenol.*, October, 1943, 50: 444.—(P. Lowy)

Rib Fractures in Atypical Pneumonia.—Eighteen cases of fractured ribs were found in a review of the films of 500 consecutive cases of atypical pneumonia; 10 of the 18 were overlooked at the time of the original examination. The patients gave no history of trauma. The site of the fractures was in the anterior axillary or in the axillary line where the muscle fibres of the serratus anterior and externus obliquus abdominis exert opposing forces. It is generally believed that these fractures are due to violent coughing spasms which frequently occur in atypical pneumonia. The severity of the pneumonic process bears no relation to the occurrence of rib fractures. There was no evidence of calcium deficit, and all fractures healed promptly.—*Rib Fractures in Atypical Pneumonia*, R. M. Harvey, *Am. J. Roentgenol.*, November, 1944, 52: 487.—(P. Lowy)

Ornithotic Pneumonia.—Three cases of atypical pneumonia apparently caused by the virus of psittacosis are presented, the literature is briefly reviewed, and the clinical, roentgenological and laboratory findings are described. After an incubation period of seven to fourteen days, signs of a generalized infection of varying severity appear, together with pulmonary involvement which in severe

cases may be wide-spread and associated with pleural effusion. Chest complaints are often disproportionately slight, and cyanosis more severe than one should expect from the roentgenographic findings. The white blood cell count is usually low or normal. The diagnosis of ornithotic infection can be substantiated by the finding of the virus during the acute phase or of complement fixing antibodies during convalescence; the titre of the latter must rise during the recovery period. Roentgenologically, the pulmonary lesions are similar to those seen in other cases of atypical pneumonia, that is, a central, patchy, migrating pneumonitis is most frequently demonstrated.—*Ornithotic Pneumonia*, A. Melamed & J. M. Fine, *Am. J. Roentgenol.*, May, 1944, 51: 548.—(P. Lowy)

Pneumonitis with Malaria.—One hundred and twenty-five consecutive patients with pneumonitis associated with malaria, admitted to Gorgas Hospital in a period from January, 1942 through May, 1943, were studied. The most important group, comprising 70 per cent of the total, consisted of young white men belonging to the military personnel. In this group the incidence of pneumonitis associated with malaria as compared with that of uncomplicated malaria was 3.7 per cent. The disease occurred mainly during the "rainy" season and corresponded in general to the peak of the incidence of malaria and also of pneumonitis. Physical signs were absent in 36 per cent of the cases. Roentgen examinations revealed a high percentage of lesions in the lower lobes and of the lobular type. Estivo-autumnal malaria and tertian malaria were associated with pneumonitis to approximately the same extent. Negative results of cultures of sputum were reported in the majority of cases in which specimens were submitted for study. The leucocyte count was usually normal or low. Chemotherapy and antimalarial treatment were employed. There was only one death, which was due to cerebral malaria. The period of hospitalization was 5 to 70 days. Pneumonitis in malaria may be classified as follows: (1) atypical (possibly

virus) pneumonitis, with inadequate response to therapy; (2) bacterial pneumonitis, with satisfactory response to sulfonamide compounds; (3) malarial pneumonitis, with favorable response to antimalarial therapy.—*Pneumonitis Associated with Malaria*, I. L. Applebaum & J. Shrager, *Arch. Int. Med.*, September, 1944, 74: 155.—(G. C. Leiner)

Right Middle Lobe Pneumonia.—In reporting the case record of a patient with an acute pneumonia of the right middle lobe, the author takes occasion to point out the value of roentgenograms taken in the lateral projection for demonstrating the location of the right middle lobe and the fissures of the lung.—*La radiología del pulmón derecho y especialmente del lóbulo medio y cisuras*, A propósito de una neumopatía aguda, M. M. del Carril, *Rev. méd. d. Hosp. Ital. d. La Plata*, June, 1944, 1: 35.—(R. Kegel)

Fleeting Pulmonary Infiltrate.—A round, fairly dense, sharply bordered infraclavicular infiltrate with no peripheral reaction is described as occurring in a 31 year old asthmatic. X-ray examination twenty days later failed to show it. The author believes it was a small atelectatic focus, provoked by a localized bronchial spasm or mucosal congestion. The differential diagnosis lies between tuberculous round infiltrate, hydatid cyst, primary or metastatic tumor and the above which is uncommon.—*Infiltrado redondo fugaz*, M. Fierro Vignoli, *Hoja tisiol.*, June, 1944, 4: 89.—(J. S. Peterson)

Fleeting Pulmonary Infiltrates.—The case histories of 2 patients with transient pulmonary infiltrates are reported. In the first patient an infiltration in the right lower lobe was followed by an infiltration in the left mid-field. The second patient had only one infiltration in the left mid-field. In both cases the eosinophils were 4 per cent and in the feces of the first patient parasites were found. In both cases the infiltrates disappeared entirely within ten days. The catarrhal upper respiratory symptoms which had been present

at the onset of this condition in both patients make it appear likely that the pulmonary infiltrations were part of an influenzal disease. (Bronchopneumonia and tuberculosis were excluded on the basis of the X-ray appearance and the clinical course.) It is assumed that previous diseases (tuberculosis in the first and Basedow's disease in the second case) had caused a vascular instability in the lungs which became clinically manifest under the influence of the influenza virus.—*Contributo allo studio degli infiltrati polmonari fugaci*, M. Mattina, *Lotta contro la tuberc.*, 1941, 12: 707.—(G. Simmons)

Fleeting Pulmonary Infiltrates.—Transient pulmonary infiltrates are classified into three different categories: (1) transient infiltrates occurring in individuals who have tuberculosis in other pulmonary districts. These processes are considered to be tuberculous epiphenomena on a vascular basis. Their resolution is relatively slow and usually takes several months; (2) transient pulmonary infiltrates associated with acute forms of different pulmonary conditions, especially pneumonia and bronchopneumonia; (3) transient pulmonary infiltrates with eosinophilia as first described by Loeffler and believed to be on an allergic basis.—*Les ombres radiologiques pulmonaires fugaces. Essai de classification et d'interprétation à propos de quelques observations inédites*, E. Delbecq & A. Garnier, *Arch. méd.-chir. appar. respirat.*, 1942, 15: 17.—(G. Simmons)

Loeffler's Syndrome.—Few if any cases of Loeffler's syndrome have come to autopsy so far, because the condition is benign and never is fatal. In this paper 4 cases of transient eosinophil pulmonary infiltrate are reported. The patients died of another cause. Macroscopically these infiltrates were not different from any bronchopneumonic focus. Microscopically the great number of eosinophil cells was striking; otherwise these infiltrates showed all the characteristics of an inflammatory process. Charcot-Leyden's crystals were found in only one case. Interesting is the presence of concomitant eosinophil infiltrates

in other organs. The problem of the origin of this condition is not yet clear, but animal parasites appear to be the main cause, especially the ascaris. Loeffler's pulmonary infiltrate is considered to be an inflammatory allergic reaction toward different antigens which can arrive in the lungs by different ways.—*Das eosinophile Lungeninfiltrat. Pathologische Anatomie und Pathogenese*, H. v. Meyenburg, *Schweiz. med. Wchnschr.*, 1942, 11: 809.—(G. Simmons)

Eosinophilic Lung Infiltrations.—A soldier of 23 was taken ill with protean symptoms of respiratory disease. Examination of the peripheral blood showed leucocytosis from 16,000 to 41,000 with up to 80 per cent eosinophils. The chest X-ray film showed bilateral pulmonary infiltrations which were fleeting in character and repeatedly resolved and reappeared. Thorough work-up failed to reveal any etiological agent, although a few ova of *Trichuris trichiura* were found in 2 out of 32 stool examinations. Sputum and urine examinations were negative for parasites or pathogenic bacteria. Intracutaneous tests for allergens, including tests for trichinella, were negative. Blood agglutination studies for brucellosis were negative and no filariae were found on examination of midnight blood smears. Sternal puncture showed a predominance of eosinophils. The patient was cured after an illness of nearly three months by the injection of biweekly doses of 0.06 g. of Mapharsen. Ten such treatments were given. This therapy was employed following a report by Weingarten from India who cured similar cases with arsenicals.—*Transitory Lung Infiltrations Accompanied by Eosinophilia*, H. Miller, *New England J. Med.*, January 4, 1945, 232: 7.—(H. Marcus)

Lung Abscess.—From the point of view of etiology, pathogenesis, prognosis and treatment, several types of lung abscess must be distinguished. The most common abscess is the solitary putrid abscess. It is caused by anaerobic organisms, notably fusiform bacilli, spirochetes, streptococci and vibriones, and it

occurs most frequently when the natural defensive mechanisms guarding the lung from infection are in abeyance, namely, during anesthesia, unconsciousness and sleep. Infected material lodges in a terminal bronchiole and there sets up a localized area of gangrene. This area enlarges until the local defense mechanisms are sufficient to wall it off, usually before the pleura is reached. After seven to ten days the contents of the infected area liquefy partially and necrotic lung slough and pus are evacuated through the bronchus. When evacuation is complete, the abscess heals spontaneously. More often only partial evacuation takes place and surgery is needed to effect a cure. Putrid abscesses following upon abdominal operations usually carry a 60 per cent mortality and it is better to leave them alone. Other putrid abscesses have a good chance for permanent cure by surgery. Aerobic abscess of the lung is the result of a diffuse bronchopneumonia. Several lesions coalesce; and usually several small abscesses are formed. The smaller ones tend to heal spontaneously upon discharging their purulent contents. The large ones may need surgical drainage, although the cures from surgery are not as dramatic in this type as in the anaerobic type. The prognosis is good. Staphylococcus abscesses occupy a special place. Multiple abscesses may occur during the course of a generalized septicemia. The prognosis is good if the patient survives his infection. Another type follows upon a staphylococcus pneumonia. Multiple lung abscesses form and the patient is extremely ill. The prognosis is grave. Occasionally hematmata following injury to the chest break down and suppurate. This is unusual, because resorption of the extravasated blood is the rule. However, when the hematoma becomes infected an abscess may form which demands surgical treatment. Bronchial abscesses are occasionally seen. They occur when the bronchus becomes occluded by a foreign body of mineral matter, such as a tooth. Collection of pus and exudate behind the obstruction forms the abscess but its location is entirely intrabronchial and the parenchyma remains

uninvolved.—*Lung Abscess, N. R. Barret' Lancet, November 18, 1944, 247: 647.*—(H. Marcus)

Suppurative Bronchopneumonia.—Suppurative bronchopneumonia is not rare. In a period of more than ten years 120 cases have been studied at Mount Sinai Hospital. The incidence of this disease shows seasonal variations similar to other forms of bronchopneumonia. It occurs in all age groups, however one-third of the patients were children under the age of 10 years. The history was usually that of an infection of the upper respiratory tract in previously healthy persons. The pathological features consist of a severe bronchopneumonia involving one, several or many portions of the lungs. Spread from primary areas appears to be chiefly by the mechanism of spillover. Varying degrees of suppuration and necrosis occur within the affected segments of lung, usually with the formation of single or multiple foci of liquefaction within areas of bronchopneumonia. If spectacular necrosis is present, the term of "necrosuppurative bronchopneumonia" is applied. Suppurative pleuritis is a frequent complication. Complete recovery or death in the acute stage is common. A chronic phase with formation of abscess or chronic interstitial pneumonia and bronchiectasis is rare. Bacteriologic examination was done from pus obtained by aspiration or at operation, not from sputum. Most frequently found were *Staphylococcus aureus*, hemolytic streptococci, pneumococci, *Streptococcus viridans*. The roentgen evidence of one or more areas of rarefaction in the midst of pneumonic infiltration was found to be pathognomonic. Tomography often only revealed the presence of areas of rarefaction. Symptoms were fever, cough, expectoration of purulent sputum, usually in large amounts, pleuritic pain. The signs are similar to those of other bronchopneumonic lesions. The following classification of the disease is given: I. Basic forms: A. Localized suppurative bronchopneumonia. B. Diffuse suppurative bronchopneumonia. II. Secondary suppurative bronchopneumonia: A. Postoperative. B. In cachexia. C.

From other predisposing causes. III. Surgical forms: A. Pulmonary abscess. B. Empyema and pyopneumothorax; (1) With proved pulmonary focus. (2) Without proved pulmonary focus. IV. Complications of suppurative bronchopneumonia: A. General: (1) Cerebral. (2) Septic. B. Local: (1) Lattice lung. (2) Bronchiectasis. (3) Pericarditis. (4) Mediastinitis. The disease is self-limited and essentially unaffected by chemotherapy or serum therapy. Surgical complications within the thorax are common. Pulmonary abscess is an unusual complication. Of these 120 cases, 29 died (24.2 per cent), mostly due to intrathoracic complications.—*Acute Suppurative Bronchopneumonia*, H. Neuhoef & A. Thomas, *Arch. Int. Med.*, January, 1945, 75: 45.—(G. C. Leiner)

Bronchiectasis.—At a Station Hospital, bronchiectasis was found to be the most frequent chronic pulmonary condition. Ninety-five patients, most of whom were admitted with acute respiratory infections, were observed for several weeks and months, and an attempt was made to correlate the prebronchographic roentgenological findings with the results of bronchography. Frank bronchiectasis was demonstrated in 37 cases, minimal or questionable bronchiectasis in 24 and no bronchiectasis in 34. Slowly resolving basal bronchopneumonia was the most frequent prebronchographic abnormality. This was found in 53 of the 95 cases observed, and in 28 of the 37 in whom later frank bronchiectasis was revealed by bronchography. Prominent pulmonary markings are even more frequently seen, but are less reliable in indicating bronchiectasis. Six of the 37 frankly bronchiectatic cases had recurrent bronchopneumonia in the same area of the lung. The finding of a shrunken contracted area of the lung also serves to raise the question of bronchiectasis; complete segmental atelectasis was not observed in this series. Although bronchiectasis may be strongly suspected from plain roentgenograms a definite diagnosis cannot be established without bronchography.—*The Diagnosis of Bronchiectasis in Young Adults*,

Prebronchographic Roentgen Manifestations Observed among Military Personnel, W. A. Evans & L. J. Galinsky, *Am. J. Roentgenol.*, May, 1944, 51: 537.—(P. Lowy)

Bronchiectasis.—The incidence, pathology, pathogenesis, bacteriology, symptomatology, course, importance and treatment of bronchiectasis are discussed in detail, in order to arrive at some means of prevention. Modern diagnostic methods reveal that bronchiectasis is not at all uncommon. Among adults, males are somewhat more frequently affected, while in children the sex ratio is about equal. The disease occurs in all age groups, the onset being before the age of 10 in half the cases; the diagnosis is most frequently made in the third decade. The clinical entity of bronchiectasis requires the presence of dilated bronchi and an associated infection; the latter is absent in so-called dry bronchiectasis. Dilatation of the bronchi is in itself the result of an infection which destroys the bronchial wall and thus produces cylindrical, fusiform or saccular bronchiectasis. If the bronchial wall is perforated in the course of the infectious process abscess cavities are formed. Bronchiectasis does not tend to spread beyond the original site of involvement; however, in the involved area the changes are progressive. The left lower lobe is most frequently affected, perhaps because of the anatomical characteristics of the left bronchial tree. It is now held probable that bronchial obstruction is essential in the pathogenesis of bronchiectasis. When inspissated secretion, tumor, granulation tissue or scarring occludes a bronchus collapse of pulmonary tissue distal to the obstruction occurs, with resulting overaeration of the surrounding lung tissue and disturbance in the normal pressure conditions. Traction is thus exerted on the weakened bronchi. In partial bronchial obstruction with ball-valve effect, the inspiratory increase in pressure may be sufficient to dilate pathological bronchi. From the etiological point of view bronchiectasis may be congenital or acquired. Among the latter chiefly infectious, chiefly obstructive and miscellaneous groups can be differentiated,

with several subdivisions in each group. There is no single organism responsible for the development of bronchiectasis. The salient clinical features are cough, expectoration and occasional hemoptysis. In addition, bouts of fever, dyspnea, night sweats, anemia and loss of weight may be present. The cough is usually worse in the morning. The sputum is frequently foul and "chunky," its amount varies. Hemoptysis is common in bronchiectasis and is due to the presence of vascular granulation tissue. Failure to eliminate bronchial secretions produces fever, the degree of which depends upon the amount retained. On physical examination there are not pathognomonic signs of bronchiectasis. Clubbing of the fingers is frequently found. The clinical symptoms and signs and the routine roentgenograms are not sufficient for the diagnosis. Bronchoscopy and bronchography are essential. The former may reveal congenital anomalies, foreign bodies or signs suggestive of bronchiectasis, although the dilated bronchi themselves usually cannot be reached with the bronchoscope. Bronchography, on the other hand, may unquestionably demonstrate the presence of bronchiectasis. Although its onset is usually during childhood, in the majority of cases, bronchiectasis does not become clinically manifest until early adult life. The patients are subject to frequent protracted "colds," and eventually toxic symptoms (lassitude, loss of weight, etc.) appear and cough and expectoration persist even between the acute flare-ups. Repeated attacks of pneumonia are apt to occur and one of these may be fatal. The mortality rate of bronchiectasis as reported in the literature varies between 23 and 38 per cent. Medical treatment consists of postural drainage and general and symptomatic measures. Bronchoscopic drainage affords but temporary relief. The value of radiotherapy in converting an infected bronchiectasis into a dry one is doubtful. Lobectomy and pneumonectomy promise to give permanent cure in cases limited to one lobe or one lung. Surgical treatment should be resorted to if the disease shows definite signs of progression, and then the

operation should be performed as early as possible, before the patient's general condition declines. More than half the cases are unilateral and thus suitable for surgical treatment. In the prevention, diagnosis and thorough treatment of infection, apt to produce bronchiectasis, are important. Such infections include the common cold, influenza, measles, whooping cough and pneumonia. Cases of pneumonia should be followed roentgenologically until complete resolution, and if this is delayed, bronchoscopic and bronchographic examination should be performed. Bronchial obstruction of whatever cause (foreign bodies, broncholiths, thick bronchial secretions, strictures, tumors) should be promptly investigated and if possible relieved. In general, roentgenography and bronchoscopy are the most important diagnostic procedures in the prevention of bronchiectasis. The proper use of these and the education of the medical profession and of the lay public are required if the incidence of bronchiectasis is to be reduced.—*A Plea for the Prevention of Bronchiectasis*, K. Kornblum, *Am. J. Roentgenol.*, March, 1944, 51: 202.—(P. Lowy)

Irradiation Pneumonitis.—A case of Hodgkin's disease treated by X-ray is described. The patient, a 52 year old white male, presented tender enlarged nodes in the supraclavicular fossae and in the left axilla. A biopsy specimen from a node showed typical Hodgkin's disease on microscopic examination. A roentgenogram of the chest showed moderate widening of the mediastinum, due to enlargement of the lymph node and slight infiltration extending into the lung tissues adjacent to the hila, which was more marked on the left side. Over a period of 9 months the patient received many X-ray treatments. At first the lung fields were shielded, but later this was discontinued. Near the end of the course the mediastinum was intensively irradiated, 3,836 r being administered over a period of 17 days. A month later he became very short of breath, with rapid respirations and slight cyanosis of the face and lips. Roentgenograms of the chest showed infiltration of

the lower two-thirds of each lung becoming increasingly dense towards the base. He was then given deep therapy to the posterior mediastinum and to the lumbar regions. Death occurred shortly, apparently from asphyxia. It is to be noted that the patient developed marked respiratory symptoms shortly after a course of irradiation to the mediastinum where the adjacent lung tissues necessarily were not shielded. Roentgenograms at this time showed an extensive pneumonitis. At autopsy the lungs exhibited lesions similar to those produced experimentally by over-irradiation. A patchy exudate composed of edema fluid, a few red and white cells, fibrin and fibrinous-hyaline membrane was found involving the greater portion of each lung. There was wide-spread organization of this exudate. A few minute microscopic foci of Hodgkin's disease were found in the bronchial lymph nodes and in the pericardium. No Hodgkin's tissue was found in the lungs. Death occurred from excessive irradiation. (Illustrated).—*Irradiation Pneumonitis: Report of a Case, T. O. Alexander, Bull. Johns Hopkins Hosp., October, 1944, 75: 199.*—(J. S. Woolley)

Hydatid Cyst.—The authors report an instance of an hydatid cyst of the spleen rupturing into a bronchus. The patient was a 32 year old married woman who entered the hospital complaining of malaise, anorexia, chills, fever, left pleuritic pain, cough and dyspnea of 40 days' duration and of abundant mucopurulent expectoration of several days. The positive physical findings were signs of a pleural effusion at the left base, an enlarged spleen, and an umbilical hernia. There was an eosinophilia of 6 per cent. Ghedini's reaction was doubtful and Cassoni's negative. There were no tubercle bacilli in the expectoration but the hooklets of taenia echinococcus were found. An X-ray film of the chest showed a marked elevation of the left leaf of the diaphragm. Laparotomy disclosed the complete destruction of the spleen by a hydatid cyst. After formol injection the cyst was marsupialized. The postoperative course

was satisfactory. Three years later the patient returned for repair of the umbilical hernia. An X-ray film of the chest showed no abnormalities. There was no eosinophilia. Both Ghedini's and Cassoni's reactions were negative. Laparotomy revealed absence of the spleen and scar formation between the tail of the pancreas and the diaphragm. There was no evidence of cyst formation in the abdominal cavity. Hydatid disease of the spleen is infrequent (3 per cent). Morel's 20 cases comprised 17 cysts primary in the spleen and 3 secondary to rupture of an abdominal cyst. Perisplenic adhesions are common especially with the diaphragm. Symptoms usually do not appear until the cyst is large.—*Quiste hidático del bazo abierto en bronquios, D. Unchalo, J. M. Mainetti & C. Cuculicchio, Rev. méd. d. Hosp. Ital. d. La Plata, June, 1944, 1: 173.*—(R. Kegel)

Bronchogenic Cysts.—The differential diagnosis between true, bronchogenic cysts and acquired lesions is sometimes impossible. The former are probably congenital and are usually situated in the mediastinum, the latter may represent the end-results of lung abscess or bronchiectasis. Various tumors of the lung and mediastinum also enter into the differential diagnosis. Fifteen cases of proved bronchogenic cyst are described. In some of them the histological picture was not quite typical of, but very similar to, that of bronchogenic cysts; in others no histological examination was done but the gross appearance of the lesion made the diagnosis practically certain. Three additional cases are presented in which the diagnosis was questionable. Roentgenologically, bronchogenic cysts appear as smooth, round or ovoid shadows which sometimes show change in shape with change in the patient's position. The demonstration of tracheal attachment of the mass and of intramural, extramucosal involvement of the esophagus corroborates the diagnosis. The cyst may or may not show a fluid level; if it does, the differentiation from lung abscess may be impossible. Clinical symptoms, if there are any, also are suggestive of lung abscess.—

The Roentgenologic Appearance of "Bronchiogenic" Cysts, L. L. Robbins, Am. J. Roentgenol., September, 1943, 50: 321.—(P. Lowy)

Cystic Disease and Dextroaortic Arch.—A 40 year old male teacher is reported, who developed a febrile acute pulmonary congestion at the right base with diffuse bronchitis. The upper zones of both hemithoraces were hyperresonant and there was no indication of pulmonary activity, contrasting with a rich clinical phenomenology in the lower zones. The patient recovered several days later. A serial radiological study revealed in the left upper and middle pulmonary zones a giant bulla of subpleural emphysema. In the right lung there was a giant air cyst and a congestive zone. There were scattered annular shadows. The aortic arch shadow was atypical, being to the right and at this level the trachea was displaced forward showing also a sinistroposition, pathognomonic of aortic dextroposition. There was coexistence of a double congenital malformation, the dextroposition of the aortic arch and the cystic disease, the former unquestionably being of embryonal origin and the latter was also considered as congenital due to: (1) its coexistence with another congenital malformation, (2) the air cyst shadows remaining unchanged after two and one-half years of observation, (3) the coexistence of some other annular shadows in the neighborhood of the giant air cysts that also remained unchanged, and (4) the absence of pulmonary diseases during the past life of the patient. In this case there was also coexistence of the two cystic types of congenital pulmonary alterations, namely, the air cyst and the bulla of subpleural emphysema.—*Disgenesia pulmonar, bilateral, de forma quística gigante y dextroposición del cayado aórtico, J. Queirel & M. Moreau, Rev. Asoc. méd. argent., January-February, 1944, 58: 14.—(J. Badell)*

Annular Shadows.—Five cases are reported in which annular shadows of uncommon type were encountered. In all the cases the onset of the disease was with evidence of infection,

at first localized (sore throat, mastoiditis, arthritis, etc.), then systemic; blood cultures were positive (for *Streptococcus hemolyticus* and *Staphylococcus aureus*, respectively) in 2 patients. Within a few days multiple rounded shadows appeared in both lung fields. Soon central rarefaction occurred, resulting in thick walled annular shadows containing air and fluid. All patients were given one or several of the sulfonamides. Four patients recovered; one of these developed areas of localized empyema which were subsequently drained, while in the 3 others several months after the acute illness the annular shadows were still visible, but by this time closely resembled emphysematous blebs. One patient died and was autopsied. On the basis of the postmortem findings, it is suggested that the origin of the annular shadows may be septic thrombosis of the bronchial artery, with resulting infarction and breakdown.—*Annular Shadows of Unusual Type Associated with Acute Pulmonary Infection, L. R. Sante & C. E. Hufford, Am. J. Roentgenol., December, 1943, 50: 719.—(P. Lowy)*

Nontuberculous Cavitation.—Although the most frequent cause of pulmonary cavitation in the upper lobes is tuberculosis, the finding of 1.5 per cent nontuberculous cavities in an autopsy material of 2,000 cases with cavitation warns that causes other than tuberculosis have to be considered in the diagnosis. Eight cases are presented, all of whom had cavitation but no tuberculosis. The 8 diagnoses were the following: anthracosilicosis, cystic disease of the lung, actinomycosis, aortic aneurysm causing pulmonary necrosis, bronchogenic carcinoma with parenchymal necrosis, lung abscess, infection with Friedländer's bacillus, bronchiectasis. In the majority of these cases tuberculosis was diagnosed at first, although only one of them had a single positive sputum.—*Non-tuberculous Pulmonary Cavitation, L. Nathanson & P. Morgenstern, Am. J. Roentgenol., January, 1944, 51: 44.—(P. Lowy)*

Interstitial Emphysema of Lungs.—There are many clinical cases in which the presence

of air in the tissues of the lung is not suspected, and in which its effects have been regarded as being produced by the primary disease itself, rather than by the interstitial air. There are many other cases in which air is recognized as being present in the pleural cavities, in the subcutaneous tissues of the neck, trunk, etc., in the retroperitoneal spaces or in the peritoneal cavity, but in which the method of escape of air and the route it followed is misunderstood. Because this air in the pulmonary interstitial tissues may cause death through airblock, if it is not removed, the clinician must become aware of the conditions which predispose to its appearance. These conditions may be divided into three categories: (1) those in which there is first an atelectasis of some part of the lung, followed by hyperinflation in adjoining regions of the same lung or in the opposite lung; (2) those in which there is a general overinflation with or without increased intraalveolar pressure; (3) those in which there is evident a decreased blood supply to the pulmonary vessels preferably either with increased intraalveolar pressure or with hyperinflation. The mode of escape of air is the same in these three classes, namely, through ruptured alveolar bases into the sheaths of the pulmonary vessels, and the clinical picture may be the same in all, with any of the following conditions either alone or in combination: air in the mediastinum; in the thoracic cavity; in the subcutaneous tissues of the face, neck, chest, axillae and body; in the retroperitoneal spaces from whence it may rupture into the peritoneal cavity; around the pericardium, in which event a pericardial knock is heard. There is dyspnea and cyanosis when the pressure in the mediastinum rises too high, limitation of respiratory movements with the chest becoming fixed in a position of maximal or submaximal inspiration when the air either distends the mediastinum or gets into the connective tissue septa of the lung. The air may gradually be resorbed and the patient recover, or it may increase in severity and the patient may die. The precipitating cause of this train of events may occur in a wide variety of conditions, but is

always a pressure gradient from air in the alveoli to perivascular sheath or underlying septa, leading to alveolar rupture and formation of pulmonary interstitial emphysema. Air leaks from the overstretched alveoli into the sheaths or adventitia of small branches of the pulmonary arteries and veins (factor A); or from alveoli, surrounding blood vessels not filled to the normal extent with blood (factor B), the alveoli being either normally expanded or hyperinflated, under atmospheric pressure or pressures above atmospheric. The bubbles of air press upon the vessels occluding their lumina producing airblock, and may leak into the interlobular connective tissue, causing airblock. It makes its way along the vessel sheaths to the mediastinum where it presses upon the large vessels at the base of the heart. It may be removed from the anterior mediastinum. It may make its way upwards into the neck, face and axillae, thence down over the chest and arms, giving rise to subcutaneous (erroneously called "surgical") emphysema. It may make its way downwards along the aorta and esophagus into the retroperitoneum and may rupture into the peritoneal cavity. Symptoms produced by air in the abdominal cavity may simulate acute abdominal conditions for which operation may be mistakenly performed. It may make its way forward over the heart, whence it may give rise to a loud crunching sound, "Hamman's sign," with each heart beat. It may travel laterally into the vessel sheaths of the other lung, or backward along sheaths of the same lung into areas in which there is no leakage. It may rupture the mediastinal wall producing pneumothorax. Collapse of the lung tends to stop the leak, except in cases in which there is violent cough. Tension pneumothorax may result from air escaping from the mediastinum, but the tension is built up not during inspiration, but during forced expiration of cough or when the glottis is closed and the intrapulmonary pressure rises above atmospheric. Air continues to leak as long as the factor initiating the original break is operative. In some instances the leak appears to be favored merely by respiratory movements, especially

if they are of a dyspneic character. The factor responsible for moving the air along the sheaths is the lengthening and shortening of the bronchi in normal respiration. Pain may possibly be caused by air pressing upon the pulmonary and mediastinal vessels, simulating angina pectoris. Circulation is interfered with by the collapse of the pulmonary vessels producing airblock, causing venous stasis and giving rise to cyanosis. Respiration is interfered with by the splinting action of the air in the connective tissues of the lung causing airblock, preventing the escape of air in expiration and giving rise to dyspnea. The heart action may be interfered with in three ways: (1) by being pressed upon by the distended lungs which prevent its filling; (2) lack of blood to fill it because of systemic and pulmonic venous congestion, arising through pressure by air bubbles on vessels, and stasis; and (3) by direct pressure upon it by air bubbles in the precordium, and in the posterior mediastinum. Factors predisposing to leakage are apparently toxins of certain infectious diseases, particularly influenza; and perhaps an inherited constitutional weakness of the alveolar walls. Once the leakage has begun, the pressure necessary to continue the leak need not be so high as that initiating the rupture. When air escapes from the mediastinum into the subcutaneous tissues, or into the retroperitoneum or even into the pleural cavities, provided that it does not produce bilateral pneumothorax, or a tension pneumothorax, the condition is likely to be benign, since the pressure in the mediastinum is relieved. If the leak continues and builds up higher pressures in the mediastinum than can be relieved by the avenues of escape, the condition, originally benign, may become malignant. It is when the air cannot escape from the mediastinum and the pressure rises too high that the condition becomes malignant. Air in the mediastinum and interstitial tissues of the lung may be occult, unrecognized by means of visible manifestations. It accompanies a wide variety of clinical conditions and respiratory diseases. Especially when it is occult it may be malignant; when it is malig-

nant it can be fatal. When its presence is diagnosed, it may be withdrawn and thus the patient's life may be saved. (Authors' summary).—*Malignant Interstitial Emphysema of the Lungs and Mediastinum as an Important Occult Complication in Many Respiratory Diseases and other Conditions: An Interpretation of the Clinical Literature in the Light of Laboratory Experiment*, Madge Thorlow Macklin & C. C. Macklin, *Medicine*, December, 1944, 23: 281.—(G. C. Leiner)

Emphysema of Lung.—Senile or postural emphysema is usually not sufficiently serious to warrant special therapy. Extreme degrees of respiratory dysfunction are seen in obstructive or so-called chronic hypertrophic emphysema. This type is seen in the young or middle aged, and there is usually a long history of chronic respiratory infections, such as bronchitis, asthma and repeated attacks of pneumonia. Diminution in function is often so extreme that patients are dyspneic even at rest. The vital capacity may not exceed 1,000 cc. and, even where the actual measurement of vital capacity appears good, there may still be extreme disability due to abnormal prolongation of the expiratory phase, so that the patient cannot utilize his capacity. Although it may not be apparent on physical examination, a spastic element is frequently present, and the therapeutic test with inhalation of nebulized adrenalin or injection of adrenalin in oil is always worth while. Oxygen therapy is of extreme usefulness in raising the oxygen saturation of blood and thus correcting the chronic state of anoxia in which these patients live. The arterial blood in a bad case may have an oxygen saturation of not more than 60 per cent. Discontinuous oxygen therapy at home is entirely practicable. It provides the patient with the much needed rest and brings about an improvement in the patient's general condition so that the amount of oxygen can be gradually reduced. In some cases abdominal belts may be useful.—*The Abnormal Physiology of Chronic Pulmonary Emphysema*, A. F. Goggio, *New England J.*

Med., November 16, 1944, 231: 672.—(H. Marcus)

Emphysematous Bullae.—A case of lung abscess in a 15 year old female is described. Although on two occasions acid-fast bacilli were found in the sputum on concentration, lung abscess was diagnosed and surgical drainage was performed. On careful examination, including guinea pig inoculation, no evidence of tuberculosis was found in the pus evacuated from the abscess or in the abscess wall. The patient steadily improved and was discharged ten months after operation. Shortly before discharge, planigrams revealed several thin-walled annular shadows at the site of the previous abscess. These shadows are believed to represent emphysematous bullae, due either to a check-valve mechanism, or to the surgical interference, or to both.—*Postoperative Emphysematous Bullae following Lung Abscess*, W. R. Oechsli, *Am. J. Roentgenol.*, August, 1944, 52: 145.—(P. Lowy)

Emphysema of Mediastinum.—The diagnosis of mediastinal emphysema is difficult. The case presented was a man, 24 years of age, who in 1940 noticed a sharp pain in his left arm and left axillary region. This pain increased with all movements. He had intense palpitations of the heart and at this time a loud pericardial friction rub was heard. The patient was X-rayed and an electrocardiogram was taken, but no evidence of any disease, pulmonary or other, could be found. Four years later he reentered the hospital complaining of a sharp pain in the lower left chest radiating into the left shoulder, of anxiety and palpitations. Three days after the onset a friction rub appeared in the precordial region and a high-pitched r  le in the left axillary region. Neither fluoroscopy nor X-ray films revealed any abnormalities. The rubbing sound over the pericardium is explained by the movements of the heart. The compression and decompression of the air present in the mediastinum causes the pulse-like rhythm. The absence of radiological signs is explained by the small quantity of air which entered the

mediastinum. The patient made a complete recovery.—*Un nuevo caso de enfisema espont  neo del medi  stino (forma frustra)*, E. G. Fong  , *Prensa m  d. argent.*, November 22, 1944, 31: 2380.—(W. Swienty)

Spontaneous Pneumothorax.—Seven soldiers with spontaneous pneumothorax were admitted to the Station Hospital at Seymour Johnson Field in a period of 12 months. The patients were at an age of 19 to 23 years. The attack was preceded by exercise in 3 cases only; it occurred during sleep in one case. The main symptom was chest pain. Physical findings were present only when the lung was collapsed more than 50 per cent. The time required for re  xpansion of the lung was 3 to 37 days. None of the patients had pulmonary tuberculosis. It is believed that spontaneous pneumothorax was produced by the rupture of subpleural emphysematous blebs. It is stressed that "recurrent bouts of chest pain, in otherwise normal, young individuals, unaccompanied by friction rub or fever, but often associated with fine crepitant r  les in the area of pain, suggest spontaneous pneumothorax and warrant X-ray study."—*Spontaneous Pneumothorax in Soldiers*, P. P. Pease, L. G. Steuer & A. S. Chapman, *Bull. U. S. Army Med. Dept.*, November, 1944, No. 82: 102.—(G. C. Leiner)

Spontaneous Hemopneumothorax.—A case is reported of a 28 year old white woman who had a copious hemoptysis and, as a therapeutic measure, a pneumothorax was induced. Collapse therapy was continued among other reasons because of positive sputum. Pneumothorax was maintained by refills performed every 12 or 14 days. The only existing adhesion was severed. The patient awakened suddenly 18 months later with an intense pain in the right lower chest accompanied with dyspnea. She had to be hospitalized, presenting all the symptoms of extreme illness, pallor, coldness, cyanosis, weak pulse, tachycardia, blood pressure 90/70. As the patient had had amenorrhea for two months a gynecological examination was done to rule out a rupture

of an extra-uterine pregnancy, but probable signs of a normal two and one-half month pregnancy were found and confirmed by the Friedman test. A therapeutic abortion was performed later by Boero's procedure. There was evidence of the existence of a collection of fluid in the right pleural cavity with deviation of the mediastinum and its organs to the opposite side and the existence of a shock syndrome with all the characteristics of an internal hemorrhage. It was confirmed by radiological examination; and an exploratory thoracocentesis revealed that there was a collection of pure blood. The intrapleural pressure was 28. The patient was very ill for the first days and there were periods of true shock with unconsciousness and marked hypothermia; the systolic pressure was 70 with no appreciable difference with the diastolic; tachypnea and cyanosis. All symptoms began to disappear after 4 or 5 days. Treatment consisted of evacuation of the pleural cavity and blood transfusion. The most likely cause of the hemothorax was the rupture of a subpleural "bullae" or "bleb". In the presence of a spontaneous hemopneumothorax there is (1) sudden diminution of breathing parenchyma due to pulmonary collapse, (2) decreasing of circulating blood due to internal hemorrhage and (3) decreasing of the functional capacity of the heart due to decreased amount of circulating blood, to shifting of mediastinum and to compression of right auricle.—*Hemoneumotórax espontáneo agudo en el curso de un neumotórax en mantenimiento: Primera comunicación mundial, R. Ballester, Rev. de tuberc. d. Cuba, October-December, 1943, 7: 503.*—(J. Badell)

Anthracosilicosis.—The case described is that of a 63 year old male who worked as a pick miner in a soft coal mine from 1884 to 1896. One month before death an X-ray film of the chest showed irregular nodulation in both lung fields with the exception of the apices, and a conglomerate density in each subclavicular region. The sputum was negative for tubercle bacilli on smear. A tuberculin test with 1:100 mg. of OT was negative.

Five weeks after admission the patient died of carcinoma of the stomach. At autopsy 200 cc. of amber colored fluid was found in the right thoracic cavity. The surface of both lungs was black. There was a large cavity in the upper lobe of each lung; the cavities were filled with foul smelling tarry fluid. Many small, hard, black nodules were scattered throughout both lungs. Histological examination revealed conglomerate and discrete hyaline fibrosis with heavy coal pigmentation. No evidence of tuberculosis or metastatic carcinoma was found. The walls of the cavities contained free silica in sufficient amount to warrant the diagnosis of silicosis.—*Liquefaction Necrosis in Bilateral Symmetrical Conglomerate Lesions of Anthracosilicosis of the Lung: Report of Case, B. J. McCloskey, Am. J. Roentgenol., July, 1943, 50: 42.*—(P. Lowy)

Pregnancy after Lobectomy.—A considerable number of pregnancies following thoracoplasty are on record, but only one case of pregnancy after lobectomy has so far been reported. The author reports a woman in whom lobectomy was performed in 1937 for bronchiectasis of the left lower lobe. This patient was delivered of a normal child in January, 1943 and, although she was in labor for more than fifty hours, no cardiac or respiratory embarrassment was noted at any time. The patient was able to return home after sixteen days and nurse her child in addition to carrying on her household duties. Respiratory impairment after lobectomy is not due to removal of one or more lobes, but to persistent compensatory overdistention of the remaining lung. This is a variable factor and a successful lobectomy or pneumonectomy cannot be regarded as sufficient reason for therapeutic abortion.—*Pregnancy after Pulmonary Lobectomy, A. G. Bryce & E. M. Mills, Lancet, December 16, 1944, 247: 786.*—(H. Marcus)

Complications after Lobectomy.—The author describes the pulmonary complications after the removal of the inferior lobe. The important factor is a quick reexpansion of the

superior lobe on the operated side which generally occurs on the third to fifth postoperative day. The movements of the diaphragm have to be normal and the pleural cavity should be free of liquid or air. A negative intrathoracic pressure must be maintained. It must be made sure that the remaining lobe is covered with elastic pleura and its bronchus patent. If it is adherent to the pleura it should be mobilized. Postoperative collapse of the superior lobe occurred almost exclusively in patients operated on for bronchiectasis. The author describes the preoperative preparation of the patient and emphasizes the necessity of a bronchoscopy and study with iodized oil six weeks before the operation, which should be done in spring or summer. As an anesthetic, he uses ether and oxygen. Individual section and ligature of the structures of the root of the lung, injection of the mucosa of the bronchus with 95 per cent carbolic acid and alcohol is done. The patient is kept for several days in an oxygen tent and is instructed to cough every hour on the first day in order to avoid accumulation of blood and mucus in the bronchus. He receives sulfadiazine, 0.03 to 0.04 g. per pound of body weight. Despite a good technique, the superior lobe does not reexpand if fluid fills part or all of the pleural cavity, if the bronchus is obstructed by secretion or if an acute pneumonitis develops. Accumulation of fluid can best be avoided by mobilization of the adhesions of the superior lobe and "washing" with oxygen. The residual pneumothorax is replaced by oxygen just before closing of the incision. Oxygen stimulates the local defense against infection and its rapid absorption favors the reestablishment of negative intrathoracic pressure and the reexpansion of the remainder of the lung. If an empyema develops, the author strongly advises against irrigation with antiseptic solutions as they are of no benefit. Atelectasis of the superior lobe develops generally on the second or third postoperative day and is caused by the tendency of the patient not to cough. Coughing eliminates the mucus and keeps the bronchus open, but is painful for the patient. In this case a curved tube is inserted into the

bronchus and permanent suction is maintained. Interstitial pneumonitis is a rare complication and results in a rapid destruction of the affected lobe. The only treatment is removal of the lobe. Sulfanilamide pre- and postoperatively prevents this complication.—*Complicaciones pulmonares en el post operatorio de las lobectomias inferiores*, O. L. de Goycochea, *Prensa méd. argent.*, September 27, 1944, 31: 1930.—(W. Swienty)

Congenital Absence of Lung.—Various theories have been offered to explain agenesis of a lung. The most plausible of them postulates that there is a developmental error of endogenous origin and consequently not only a primary defect in the pulmonary-vascular and respiratory system but also other abnormalities of development. The formation of the lungs from two lung buds on the ventral surface of the esophagus begins in the 3 mm. embryo; therefore, complete absence of a lung is the result of a developmental defect occurring early in fetal life. Three groups can be distinguished: (1) true aplasia (no lung, bronchus or blood supply); (2) primordial bronchial bud without lung tissue; and (3) extreme hypoplasia. In the two latter groups the developmental error occurs at a later stage of embryonic life. The majority of cases reported belong in the first group. Two of the authors' 5 cases fell in the first, 3 in the second group. Agenesis of a lung may be asymptomatic and difficult to discover on physical examination. The space of the absent lung is usually filled with heart, thymus and other mediastinal structures, sometimes also with fluid. Roentgenograms reveal a homogeneous shadow on the affected side, displacement of the heart and mediastinum, elevation of the diaphragm and narrowing of intercostal spaces. In the diagnosis, bronchoscopy and bronchography are essential. The prognosis is guarded, since it depends not only on the effects of the absence of one lung, but also on the possible presence of other serious congenital anomalies. Five cases are reported; 4 of these are living an essentially normal life, while the fifth died of pneumonia.

Other anomalies of the tracheobronchial tree are recognized with increasing frequency as bronchograms become more commonly employed. Five cases illustrative of varying degrees of abnormalities of the tracheobronchial system are presented.—*Congenital Absence of the Lung (Agenesis) and Other Anomalies of the Tracheobronchial Tree*, C. F. Ferguson & E. B. D. Neuhauser, *Am. J. Roentgenol.*, November, 1944, 52: 459.—(P. Lowy)

Pulmonary Disease and Mega-Esophagus.—Five cases of pulmonary disease (abscess, bilateral aspiration pneumonitis, diffuse fibrosis and bilateral bronchiectasis) associated with mega-esophagus are reported. It is stressed that mega-esophagus may be nearly or entirely asymptomatic and its presence may be overlooked if respiratory symptoms are in the forefront. On the plain chest roentgenogram, mega-esophagus causes a widening of the mediastinal shadow to the right; in cases of pouch formation in the esophagus the border of the mediastinal shadow may be scalloped or lobulated. Sometimes a fluid level is observed in the dilated esophagus, or a double air column (trachea and esophagus) may be seen overlying the upper dorsal spine. In the lateral view the trachea is displaced anteriorly. When any of these signs are present, studies by means of a contrast medium are called for. The occurrence of the pulmonary diseases mentioned earlier may be explained on the basis of nocturnal regurgitation and aspiration of food particles stagnating in the esophagus. The causal relationship between this pathogenetic mechanism and bronchiectasis is not generally accepted. Since it appears that the association of mega-esophagus and various pulmonary diseases is not merely coincidental, careful investigation of patients with mega-esophagus or with pulmonary disease of unknown etiology is warranted.—*Pulmonary Disease Associated with Mega-Esophagus*, H. S. Weens, *Am. J. Roentgenol.*, November, 1944, 52: 472.—(P. Lowy)

Foreign Bodies.—Aspiration of vegetable foreign bodies (peanuts, various types of

seeds, etc.) is most common between the ages of 17 and 27 months. When the foreign body reaches the larynx it causes a violent laryngospasm; this is followed by forceful inspiration which draws the foreign body into the tracheobronchial tree. In suspected cases the parents should be questioned as to a history of choking. Roentgenograms are valuable only if they are positive and not misinterpreted. Among physical signs the presence of a wheeze is of the greatest importance; asthmatoïd râles, tympanitic percussion note, diminished or absent breath sounds are suggestive. In a certain number of cases the picture of the "drowned lung" rapidly develops and becomes fatal unless the foreign body is removed bronchoscopically. In less fulminating cases emphysema, atelectasis, lung abscess, bronchiectasis or empyema may follow. All these serious consequences can be prevented by early bronchoscopy. Sedatives, narcotics and cough mixtures should not be used if the presence of a foreign body is suspected.—*Vegetable Foreign Bodies in the Tracheobronchial Tree*, P. G. Bunker, *Journal—Lancet*, November, 1944, 64: 369.—(P. Lowy)

Pilocarpin in Diseases of Lung.—Injection of pilocarpin causes a pulmonary vasoconstriction. The chest X-ray film appears clearer and pathological changes become more clearly delimited from surrounding normal pulmonary tissue. Therapeutically, pilocarpin causes decrease of sputum, cough, night-sweats and dyspnea. This drug is particularly valuable in bronchiectasis, but good results may be obtained in pulmonary tuberculosis also if pilocarpin is used as an adjunct to general treatment.—*Die Pilocarpin-behandlung der Lungenerkrankungen*, V. Papilian, I. Ursu, N. Mihail & F. Antonescu-Mazilu, *Wien. med. Wchnschr.*, 1942, 1: 259.—(G. Simmons)

Fibrolipoma of Lung.—In the case described the patient suffered for twenty-two years from dyspnea and mucopurulent expectoration every winter. The sputum was always negative for acid-fast bacilli. The sedimentation rate was 76 mm. in one hour. In the X-ray

film the right hemithorax was completely obscured and opaque and there was evidence of cavity formation in the apex. A tentative diagnosis of far advanced pulmonary tuberculosis and bronchiectasis was made. On autopsy the right lung was fibrolipomatous throughout. Only in small and rare areas could normal pulmonary tissue be found. Microscopically, there was a typical lipoma, with infiltration of lymphocytes and plasma cells. Many tuberculous nodules with caseation, calcification and even bone formation were present. This ossification is evidence of progressive metaplasia. A few Langhans cells were found. Many large and small foci of fatty tissue were found throughout the lung. In the authors' opinion, the fat formation is due to the prolonged inflammatory process, and is a sign of temporary or even definite healing of the tuberculous process.—*Fibrolipomatosis pulmonar de sustitucion (a proposito de una observacion)*, P. I. Elizalde, R. I. Latienda & L. L. Boffi, *Rev. Asoc. méd. argent.*, May 15, 1944, 58: 282.—(W. Swienty)

Bronchopulmonary Tumors.—The differentiation of bronchopulmonary tumors and their early diagnosis is now more important than before, as pulmonary surgery has reached its present height. A group of malignant tumors of the large bronchi is described. They are known as "carcinoids" (or bronchial adenomata), "scar-cancers" and "carcinosarcomata." The pathologico-anatomical findings of one case of each are described. The bronchial adenoma extended into the free lumen of the left main bronchus, which it occluded, and caused the collapse of the lung. Neoplastic cells were arranged in alveoles. There was little anaplasia with rare mitosis. Some cavities invested by the typical ciliated epithelium of the bronchial wall were found. The central zone of the tumor was ossified. All this is evidence that the tumor was originally benign but had suffered malignant transformation. There were no metastases within the lung tissue, but metastases with typical bronchial and alveolar arrangement were found in the liver. The development of the tumor is slow.

It is encapsulated and grows by direct invasion. The "scar cancer" was found at the site of an anthracotic subpleural scar. The scar tissue was surrounded by neoplastic cells which invaded the pleura. It is evident that this neoplasm developed in a tuberculous scar and infiltrated the bronchi from there. There were metastases in the thoracic lymph nodes and in the opposite lung. This latter was probably implanted by aspiration. The "carcinosarcoma" developed in the right main bronchus. The tumor was not pedunculated, obstructed the main bronchus completely and penetrated deeply into the trachea. The tumor was surrounded by an exudate of leucocytes. Its main part consisted of sarcomatous tissue which was very richly vascularized. The neoplastic cells were polymorph, fusiform and had vesicular nuclei. On the surface of the tumor small zones of typical squamous carcinoma were found. These are real carcinosarcomata with anaplasia. The primary carcinoma is changed into a sarcoma.—*Contribucion anatomopatologica al estudio de los tumores broncopulmonares*, J. G. Warcalde, *Rev. Asoc. méd. argent.*, September 30, 1944, 58: 793.—(W. Swienty)

Cancer of Lung.—A statistical study was made of 100 cases of histologically proved cancer of the lung. The male-female ratio was more than 7 to 1. The largest number of cases (36) occurred in the sixth decade; the youngest patient was 26 years old, the oldest 78. Cough, fever and weight loss, in this order, were the symptoms most frequently complained of; dyspnea, chest pain, hemoptysis were also common. Fifty-five of the cases were bronchoscoped, and in 39 (71 per cent) of these the tissue removed was reported as carcinoma. Roentgenography, on the other hand, is never absolutely diagnostic, only suggestive. Thirty-two thoracotomies were done, but only 7 radical operations were possible and only 2 of these could be considered successful. Of 7 aspiration biopsies attempted 5 gave positive results, but the procedure is often technically difficult. Roentgenographically, the central type originating in the main

or primary bronchi was the most common; these tumors cause bronchostenosis, with resulting collapse pneumonitis and suppuration distal to it. The other four types, in the order of their frequency, are the following: peripheral, superior sulcus, segmental and diffuse. The average survival time was 245 days. Metastases were most common in the regional lymph nodes, pleura, bones, retroperitoneal lymph nodes and adrenals. Thirty-four cases were given radiotherapy, with symptomatic relief in 10 of them. Fifty per cent of all patients had epidermoid carcinoma, 18 per cent adenocarcinoma, 32 per cent undifferentiated tumor.—*Primary Cancer of the Lungs*, K. L. Mitton & N. M. Hardisty, *Am. J. Roentgenol.*, May, 1944, 51: 555.—(P. Lowy)

Tumor of Lung.—During a period of four years 9 patients were seen who were referred to a psychiatrist and/or neurologist since they suffered from violent neuralgic pains with a negative hysterical depression. All patients had a markedly raised blood sedimentation rate. A diagnosis of malignant pulmonary growth was established by radiologic examinations or autopsy findings. The psychological symptoms and the diffuse neuralgic pains are due to a toxic disorder of the nervous system; localized neuralgic pains may be caused by pressure from the tumor itself or from metastases. The triad of violent neuralgic pains with a negative hysterical depression and an elevated blood sedimentation rate demands an immediate roentgenological examination of the lungs.—*The Initial Neurologic and Psychiatric Syndrome of Pulmonary Growth*, A. M. Meerloo, J. A. M. A., October 28, 1944, 126: 558.—(H. Abeles)

Bronchial Carcinoma.—Of 5,515 necropsies performed in the Department of Pathology of the University of Chicago in the forty years from 1902 to 1941, 126, or 2.3 per cent, revealed primary carcinoma of the lung. These constituted 7.6 per cent of all malignant tumors, being fifth in frequency, and 10.3 per cent of carcinomata, being third in frequency. Expressed in terms of percentage of all tumors,

primary carcinoma of the lung showed a slight increase in males but not in females over the period studied; the increase was less than that of carcinoma of the colon and intracranial tumors, but greater than that of carcinoma of the pancreas and stomach. When the crude figures were corrected for changes in the annual number of necropsies, for the increase in tumors of all kinds among the necropsy population and for the shift in sex ratio and average age of this same population, it was seen that the increase was apparent rather than real. The only variable which could not be controlled, namely the shift in the type of patient admitted, can easily account for the slight increase noted.—*Increase of Primary Carcinoma of the Lung with Special Reference to Its Increase*, P. E. Steiner, *Arch. Path.*, March, 1944, 37: 185.—(D. G. Freiman)

Bronchial Cancer.—In bronchogenic tumors the shadow seen on the roentgenogram is usually larger than the tumor itself, owing to atelectasis distal to the neoplasm. Sometimes, however, emphysema instead of atelectasis is produced. A 44 year old male is described. He was admitted complaining of fever and cough, productive of purulent sputum. An X-ray film of the chest revealed a density in the upper two-thirds of the left lung. The diagnosis was unresolved pneumonia; sulfonamide was given, and a month later the density was smaller. One year later the patient complained of dyspnea, cough, stridor and pain in the left chest. A roentgenogram disclosed a density in the region of the left apex. On bronchoscopy a tumor was found in the left main bronchus; histological examination revealed squamous cell carcinoma. Pressure readings in the left pleural space were plus 8, minus 6. On exploration the left upper lobe was found to be atelectatic, the left lower lobe tremendously emphysematous. The tumor was inoperable. The sequence of events was probably as follows: partial atelectasis of the left upper lobe, complete atelectasis of left upper lobe, obstructive emphysema of left lower lobe.—*Obstructive Phenomena Associated with Primary Bron-*

chial Cancer, W. J. Ozlin, I. A. Bigger & P. P. Vinson, Am. J. Roentgenol., August, 1943, 50: 207.—(P. Lowy)

Bronchial Cancer.—Opinions differ as to the usefulness of roentgen therapy in prolonging the life of patients with bronchogenic cancer. The author treated 167 cases, and compared the survival time with that of 119 untreated cases. The survival time was calculated from the time of making the diagnosis. All cases were microscopically proved. The total dose varied from 1,250 r to 13,750 r; those patients who received more than 2,500 r had more than one course of treatment. The technique of irradiation varied considerably. All but one of the untreated patients died within nine months, none of them was alive after one year. In the treated group, 18 patients lived one year or longer, one being alive after six years. Ninety-four per cent of the untreated and 67 per cent of the treated cases died within six months. It is concluded that roentgen therapy apparently has some life-prolonging effect in bronchogenic cancer, and therefore every patient with inoperable carcinoma of the lung should be given the benefit of this treatment.—*Roentgen Therapy for Bronchiogenic Cancer, B. P. Widmann, Am. J. Roentgenol., January, 1944, 51: 61.—(P. Lowy)*

Diagnosis of Bronchial Cancer.—The search for cancerous cells in the embedded expectoration is a simple and important method in the diagnosis of pulmonary cancer. In 137 cases studied, 32 showed positive findings. Care must be taken to use true expectoration of bronchopulmonary source and fix it immediately. Microscopic diagnosis is based principally on the larger size of the cancerous cells (except in the case of the so-called cancer of small cells), the character of the protoplasm and the pathological changes of the nucleus (increase in size, more marked pigmentation, irregularity, etc.). The latter pathological changes are the most important. Generally cancerous cells are isolated and not in groups, but nevertheless permit diagnosis. Only

when the pathology of the cells is typical should the finding be considered positive. Only in this way can the diagnostic errors be kept at a minimum. In 439 cases which were not cases of pulmonary cancer, positive findings were erroneously shown in the expectoration of 6 cases. Therefore the pathologist must study the case on the basis of its clinical findings and repeat the examination in doubtful cases. This experience leads to the belief that the search for cancerous cells in the embedded sputum is as valuable as well as a simple method in the diagnosis of cancer of the lung. This method should, therefore, be used widely in all cases of bronchopulmonary diseases, the etiology of which is not absolutely clear. This should be done even in the cases of young patients, even if there are no clinical symptoms of cancer.—*Importancia de la inclusion de esputos para el diagnostico del cancer broncopulmonar, R. A. Izzo & L. Irigoyen, Publ. d. Centro Investig. Tisiol., 1943, 7: 323.—(H. Behm)*

Plasmocytoma of Lung.—A case of solitary plasmocytoma in the lung of a 30 year old Italian housewife is reported. Following a spontaneous abortion and several weeks of low-grade fever, a mass was discovered in the lung. At the time of admission to the hospital the patient was entirely symptomless. Roentgenographic examination revealed a round, sharply circumscribed, dense shadow about 5 cm. in diameter in the upper and mesial portion of the left pulmonary field. The skull and long bones were negative. The urine was negative for Bence-Jones protein. A left upper lobe lobectomy was performed and was followed by an uneventful convalescence. A well encapsulated, firm, resilient, pearly gray mass was present in the mesial portion of the lobe anterior to the hilar bronchi and vessels. On microscopic examination the predominant cell was indistinguishable from the typical plasmocyte; mitotic figures were rare. Scattered groups of lymphocytes were present, especially just beneath the capsule, and clusters of foamy macrophages were also seen. Moderate numbers of acido-

phile hyaline droplets (the so-called Russell bodies) were found throughout. The site of origin of the tumor was not determined.—*Plasmocytoma of the Lung*, J. Gordon & G. Walker, *Arch. Path.*, March, 1944, 37: 222.—(D. G. Freiman)

Carcinoma of Trachea.—A 61 year old male lecturer suffered from frequent episodes of coughing with blood-streaked sputum and fatigue over a period of three years. When he developed wheezing which reduced his voice to a whisper he sought medical care. Bronchoscopic examination revealed a tumor just above the carina which extended over the whole cartilaginous portion of the trachea. A biopsy was taken and it was reported as primary carcinoma of the trachea but the possibility of neoplastic thyroid tissue could not be ruled out. Examinations with radioactive iodine ruled out the presence of normal thyroid tissue in the area from which the tumor originated. However, the lack of storage of radioactive iodine in the tumor did not exclude a carcinoma of the thyroid. In five bronchoscopic sessions as much tumor as possible was removed. This was followed by treatment with radium in a special applicator placed through the bronchoscope. Two years after the treatment the patient was well; there was no subjective or objective evidence of tumor or metastases. The only finding was a little thinning of the mucous membrane in the area previously occupied by the tumor.—*Primary Carcinoma of the Trachea; Treatment with Intratracheal Radium; Radioactive Iodine Fails to Show Thyroid Origin*, P. H. Pierson, *J. A. M. A.*, September 23, 1944, 126: 206.—(H. Abeles)

Mediastinal Tumors.—The preoperative classification of mediastinal tumors has proved difficult or impossible, but has become increasingly important. Forty-four cases of proved mediastinal tumors were reviewed to determine, if possible, whether any of these tumors had characteristic roentgenological features. It was found that with present methods of X-ray examination no exact differentiation is

possible. However, certain diagnostic features have been demonstrated. Bronchogenic cysts are round or ovoid tumors located anywhere within the mediastinum without evidence of calcification or bone erosion. Dermoid cysts and teratomata appear as slightly more irregular masses located in the anterior mediastinum which may contain areas of calcification. Neurogenic tumors are usually smooth in outline, homogeneous in density and may be located in any portion of the mediastinum. Bone erosion is commonly associated with this type of tumor. The outstanding finding in intrathoracic goitre is its attachment to the trachea, often with associated displacement of the latter. Parathyroid and thymic tumors may be recognized as mediastinal tumors, but their character is largely dependent upon other roentgenological or clinical characteristics. Diagnostic pneumothorax might help to determine the location of a tumor, and a trial dose of X-ray may also aid in suggesting the final diagnosis. Careful fluoroscopic study and postero-anterior and lateral films should, of course, be obtained.—*Roentgenologic Features of Mediastinal Tumors*, L. L. Robbins, *Radiology*, August, 1944, 43: 115.—(G. F. Mitchell)

Mesothelioma of Pleura.—A 25 year old woman was admitted to the hospital with a six months' history of lassitude and pain over the left shoulder. Shortly before admission she developed pain in the left chest anteriorly, unaffected by breathing. Physical examination revealed shift of the mediastinum to the right, and, on the left, absent vocal fremitus, flat percussion note from apex to base posteriorly, and bronchial breath sounds. There was marked clubbing of fingers and toes. Clear yellow fluid, negative for tubercle bacilli and tumor cells, was aspirated from the left chest. Dyspnea, not present at the onset of illness, became progressively more severe, and the patient eventually died in respiratory failure. Autopsy revealed a compressed left lung entirely surrounded by a thick, firm gray sheet of tumor displacing it upward and medially. The tumor covered the entire

parietal surface of the left chest wall and was adherent to the diaphragm and pericardium. On section the tumor was gray-white with scattered tiny cystic areas filled with mucoid material; the consistency was almost cartilaginous. Small plaques of tumor were found on the right visceral pleura and around the hilar portion of the right pulmonary artery; tumor nodules were also present in the right lung and over the parietal and visceral surfaces of the peritoneum. Histologically, the tumor was relatively acellular and avascular. In scattered areas cells were seen with nuclei of varying shape and eosinophilic cytoplasm with indistinct outline; the stroma was eosinophilic and fibrillar, arranged in an interlacing and whorled pattern, and rich in reticulum. Signet ring cells were present in moderate numbers and were most numerous in the collagenous portions of the tumor; fat and mucicarmine stains were negative, suggesting that these cells were degenerative rather than secretory. The most striking feature of the tumor was the presence of an atypical osteoid matrix in the central portions, a finding which does not appear to have been previously reported in a case of pleural mesothelioma.—*Mesothelioma of the Pleura*, A. V. Postoloff, *Arch. Path.*, April, 1944, 37: 286.—(D. G. Freiman)

Hodgkin's Disease.—Of 55 proved cases of Hodgkin's disease intrathoracic involvement was found in 35 (63 per cent). The latter were classified into five types: mediastinal, parenchymal, pleural, osseous and cardiac. In all these types the character of the disease is determined by the location and the degree of involvement of the lymphoid tissue. Fifty per cent of the cases belonged in the mediastinal group in which discrete or confluent enlargement of the mediastinal lymph nodes is seen roentgenologically. Involvement of the lung parenchyma occurred in 40 per cent of the series. In these cases the differential diagnosis from tuberculosis, pneumonia, bronchogenic carcinoma, sarcoidosis, abscess and metastatic tumor may be difficult. The invasion of the lung parenchyma may occur from

the mediastinal nodes, producing the picture of a solid growth, or the infiltration may spread along the peribronchial and perivascular lymphatics in which case linear densities are seen extending into the lungs from the hilum. In other cases the disease extends through the alveoli, thereby producing a granulomatous consolidation of lobar or lobular character. Nodular lesions are uncommon and were not observed in this series. Bronchogenic carcinoma is simulated if invasion of the bronchi causes bronchial obstruction and atelectasis, while necrosis followed by cavitation raises the question of tuberculosis, lung abscess or carcinoma. The clinical symptoms and signs of parenchymal disease (cough, chest pain, fever, night sweats, weight loss) are not diagnostic. In pleural involvement nodular or infiltrating masses are present on the pleura, usually associated with serous effusion. Involvement of the bones forming the thorax results from direct extension from lymphoid tissue; occasionally the osseous lesions are primary. Rarely, infiltrations extend from adjacent structures into the heart. Twenty-three of the 35 cases of intrathoracic Hodgkin's disease were given radiotherapy, and 17 of these showed definite improvement.—*Intrathoracic Hodgkin's Disease*, S. E. Wolpaw, C. S. Higley & H. Hauser, *Am. J. Roentgenol.*, October, 1944, 52: 374.—(P. Lowy)

Cystic Fibrosis of Pancreas.—Pulmonary changes (bronchitis, bronchopneumonia, bronchiectasis, atelectasis) are present in the great majority of patients with cystic fibrosis of the pancreas. They are probably due to vitamin-A deficiency resulting from faulty fat absorption; according to another view, the pulmonary picture is based on a coexisting congenital abnormality of the pancreas and lungs. Absence of pancreatic enzymes in the duodenal contents, steatorrhea and low vitamin-A absorption curve are the salient diagnostic features of the disease. The vitamin-A deficiency produces epithelial damage and infection in the lungs; roentgenologically, there are increased, mottled densities in

the hilar regions and streaking and mottling towards the periphery. The consequences of infection are atelectasis and bronchiectasis. Although the pulmonary changes are strikingly similar in cases of cystic pancreatic disease, yet they are not in themselves diagnostic. Similarly, hypomotility associated with dilatation of the small intestine is suggestive but not pathognomonic of the disease.—*Pulmonary Changes in Chronic Cystic Pancreatic Disease*, G. J. Baylin, *Am. J. Roentgenol.*, September, 1944, 52: 303.—(P. Lowy)

Spontaneous Paralysis of Diaphragm.—The author reviews the literature on spontaneous paralysis of the diaphragm. A few are congenital, most are acquired. Inflammatory processes of the hilar lymph nodes and cardiovascular diseases may cause pressure and atrophy of the phrenic nerve and so a paralysis of the diaphragm. The same is true for degenerative process of the muscle or of the pleural covering of the diaphragm, intestinal tumors or a change in the equilibrium between thorax and abdomen. The most common cause is tuberculosis. A systematic X-ray examination would show a far greater number of diaphragmatic paralyzes than is generally conceived. The hilar nodes must be very large if they cause pressure on the phrenic nerve. In the author's opinion, this should not be very frequent, especially on the left, as the left phrenic nerve passes far in front of the hilar nodes. He believes that there is in reality a paralysis of the muscle which occurs as a defensive reaction of the diseased hemithorax and has no relation to the enlarged hilum. The transmission of a motor reflex stimulated by the viscera may be the reason for the paralysis. This would explain diaphragmatic paralysis in cases of tuberculosis with only slight enlargement of the tracheo-bronchial nodes. Pressure on the sympathetic ganglia and the cervical plexus by tuberculous nodes is also of importance. In the review of the etiology, poliomyelitis, hysteria, syphilis, diabetes, alcoholism, rheumatism and gout as well as trauma are of importance. The symptoms of paralysis of the diaphragm are

dyspnea and polypnea, asphyxia, difficult, low speech and the sensation of the abdominal viscera moving into the thorax. The X-ray picture shows a raise of the dome of the diaphragm, diminished transparency of the lung tissue, blotting of the costodiaphragmatic angle, paradoxical movement of the diaphragm and shifting of the mediastinum to the non-affected side. A transitory paralysis of the diaphragm may be mistaken for pleurisy or pneumonia. The author describes one case.—*Contribucion al estudio de la parálisis diafragmática espontánea*, C. W. Grobli, *Prensa méd. argent.*, September 6, 1944, 31: 1764.—(W. Swienty)

Hemidiaphragmatic Paralysis.—A man was seen in whom a paralysis of the medial and anterior portion of the right hemidiaphragm was present as a remainder of an old anterior poliomyelitis. Neurological examination revealed that the left side of the cervical cord was more affected than the right; apparently there was a crossing of the phrenic nerves in the spinal cord. Scoliosis to the contralateral side and considerable damage of respiratory reserve were found.—*Partial Paralysis of a Hemidiaphragm*, H. Abeles & G. C. Leiner, *Am. J. Roentgenol.*, May, 1944, 51: 572.—(P. Lowy)

Congenital Absence of Ribs.—Complete absence of ribs may be divided into three groups: (1) absence of one rib unilaterally or bilaterally; (2) aplasia of two or more ribs unilaterally; (3) a miscellaneous group. Any of these categories may be associated with anomalies of the vertebral body. Illustrative cases of each category are recorded. The embryology of the rib and vertebral body is presented. The theories of etiology of complete aplasia of ribs are discussed. (Author's Summary)—*Congenital Absence of Ribs*, B. N. E. Cohn, *Am. J. Roentgenol.*, November, 1944, 52: 494.—(P. Lowy)

Cardiac Arrhythmia.—In the evaluation of cardiac arrhythmia in pulmonary disease, anatomically adjacent factors should be con-

sidered. Otherwise they are significant of the problem of cardiac arrhythmias in general. At times they constitute the sole evidence of cardiac disease, but often occur in the absence of such disease. One is justified in correlating their occurrence with existing extracardiac factors, and the clinician may be influenced in his prognosis and therapeutic approach by consideration of this etiologic dependence. In pulmonary tuberculosis, extracardiac factors that may produce abnormal cardiac rhythm may be (1) the influence of tuberculosis on the intravascular pulmonary tension, (2) involvements of pericardium and myocardium from adjacent pulmonary tissue, (3) toxic influences of the disease upon the heart, (4) mechanical involvement of the heart and great vessels due to torsion and displacement and (5) reflexes due to disturbed anatomy and physiology. The electrocardiograms of 1,000 cases admitted to Sea View Hospital are reviewed. In 78 there were arrhythmias; 12 of these were sinus arrhythmia, 22 were premature auricular contraction and ventricular contraction, 14 were various types of auriculoventricular conduction impairment, mostly first stage heart block, 20 were intraventricular conduction impairment and 10 were miscellaneous arrhythmias. When tabulated according to disease, it was noted that there were four times as many cases of arrhythmia in the active as in the inactive group. When studied in relation to age and cardiac disease, it was found that sinus arrhythmias occurred in the younger age group with one exception, premature contractions were equally divided in age groups, and most had evidence of cardiac disease. In the group with miscellaneous arrhythmias there was evidence of cardiac disease in all but one and most were in the older age group. Intraventricular and auriculoventricular conduction impairments predominated in those with associated cardiac disease. Evidence of cardiac disease consisted of objective criteria, for example, history of syphilis or rheumatic fever, physical findings such as peripheral sclerosis or unmistakable cardiac murmurs indicative of mitral or aortic disease, X-ray evidence of cardiac enlargement, and

typical electrocardiogram changes indicative of coronary artery occlusion. Most of those showing the auriculoventricular block occur in the younger group, but in only 3 was there no evidence of cardiac disease other than an abnormal electrocardiogram. All 3 (aged 48, 18 and 32) had a mediastinal shift. It is possible that mediastinal displacement can alter the configuration of the P wave producing a picture of first-stage heart block, but it is also possible that toxic influences may play a rôle. The effect of mediastinal displacement on the irritability of the myocardium has been stressed by a number of foreign writers, and Brumfield in this country reported 7 with extrasystoles in 15 cases of mediastinal distortion. There may be a higher percentage in this group (22) as only one electrocardiogram was made, but only one per cent of the group gave no evidence of intrinsic heart disease. This incidence is small compared to the number with mediastinal distortion seen at Sea View. As far as is known only one other large series of pulmonary tuberculosis cases thus studied has been reported. While evidence points to intrinsic cardiac disease as the etiologic factor in producing arrhythmias, the results suggest that extracardiac factors may play a rôle in precipitating these arrhythmias. The side of involvement seems to be no factor. It is conceivable that where there is mediastinal torsion, the relationship and course of the cardiac nerves may be disturbed producing increased irritability of the myocardium. The authors conclude that pulmonary tuberculosis does not affect the incidence of abnormal cardiac rhythm or abnormalities in the conduction mechanism and that in most cases other clinical or laboratory evidence of intrinsic cardiovascular involvement can be elicited. However, right pulmonary lesions involving the mediastinum may constitute an extracardiac factor in the causation of the arrhythmias and conduction abnormality in a previously diseased myocardium.—*Cardiac Arrhythmias in 1000 Cases of Pulmonary Tuberculosis*, T. T. Fox & A. L. Bobb, *Am. J. M. Sc.*, August, 1944, 208: 201.—(G. F. Mitchell)

✓ **Hemoptysis in Mitral Stenosis.**—In mitral stenosis large hemoptyses can occur the source of which is not understood. A method for injecting the bronchial veins of lungs, fresh from autopsies, is described. This method indicates the presence of direct venous connections between the bronchial and pulmonary veins in men of all ages. Mitral stenosis causes dilatation of the bronchial veins in the submucosa of the larger bronchi as a result of the establishment of a collateral flow through them. In cases of mitral stenosis in which infarction and acute pulmonary edema are not present, hemoptysis is probably due to bleeding from these dilated veins. Age, hypertension, and arteriosclerosis do not affect the bronchial venous bed, but some dilatation occurs in chronic congestive heart failure of long standing, although the only lesion of the mitral valve may be dilatation of the valve ring.—*Varices of the Bronchial Veins as a Source of Hemoptysis in Mitral Stenosis*, F. C. Ferguson, R. E. Kobilak & J. E. Deitrick, *Am. Heart J.*, October, 1944, 28: 445.—(G. C. Leiner)

Anomaly of Pulmonary Artery.—An autopsy finding offered the opportunity of studying a rare vascular anomaly in the wall of the left pulmonary artery in a female who, though she was 88 years old, had no other vascular alterations in the lesser circulation, and died of postoperative peritonitis after a colectomy. Opening the artery lengthwise near the first branching, an engorged curved vessel was seen clearly outlined through the endothelial lining, 20 mm. long, with two small branches in the convex side. No other analogous arrangement was found in the rest of the artery. The vessel, raising the inner lining, was located in the intima and serial sections revealed that, in some places, it was

in the *tunica media*. There was also a vascular net with vessels of different calibres and structure, ranging from the arterial type to ample canals, that was traced through the different layers of the artery and was connected directly with the *vasa vasorum* and with the lumen of the artery, opening by means of ostial orifices in the intima, supplied with valve-like flaps. This fact suggested that the blood-stream ran from the *vasa vasorum* toward the lumen of the artery. The absence of inflammatory or other lesions that could explain the presence of this arrangement suggested that it was congenital.—*Raro dispositivo vascular en la pared de la rama izquierda de la arteria pulmonar*, D. Branchetto-Brian & E. F. Lascano, *Rev. Asoc. méd. argent.*, March, 1944, 58: 105.—(J. Badell)

Adrenal Amyloidosis.—During the past eleven years amyloidosis of the adrenals was seen in 354 cases on autopsy at Sea View Hospital. Amyloidosis of the adrenal increases the consistency, size and weight of the organ. The zona fasciculata is involved first, the zona glomerulosa last. In none of the cases was there clinical evidence of Addison's disease. An attempt was made to find signs of adrenal insufficiency: The salt restriction test shows—in the absence of edema—fairly close correlation between the amount of chloride excreted and the extent of amyloidosis. Blood pressure, changes in renal function and carbohydrate metabolism, adynamia and gastrointestinal disturbances are of little or no assistance. In severe amyloidosis of the adrenals the body temperature is usually only slightly elevated or even normal in spite of active disease.—*Adrenal Amyloidosis*, Marguerite G. Stemmerman & O. Auerbach, *Arch. Int. Med.*, November, 1944, 74: 384.—(G. C. Leiner)

INDICATIONS FOR INTRAPLEURAL PNEUMONOLYSIS¹

A Review of 567 Thoracoscopic Examinations

H. AUBREY JONES

The objective of pneumothorax in the treatment of pulmonary tuberculosis is the relaxation of the diseased lung. The attainment of this objective is frequently prevented by pleural adhesions and, when this is so, there are three possible lines of procedure.

- 1: The adhesions may be ignored and the pneumothorax maintained. Crushing of the phrenic nerve may be added if desired.
- 2: The pneumothorax may be terminated. Treatment will then be bed-rest with or without crushing of the phrenic nerve or thoracoplasty.
- 3: The adhesions may be severed or otherwise detached.

Ideally, a pneumothorax should be free of adhesions in order to ensure optimum lung relaxation. Accordingly, if all adhesions could be detached with little danger of serious operative complications no problem would exist; intrapleural pneumonolysis would be routine. Unfortunately this is not so. While it is true that many adhesions can be severed without fear of complications there are others that can be freed only at considerable risk. This article is primarily concerned with the question of when and when not to sever such adhesions. Conclusions reached are based on results and observations of 509 consecutive closed intrapleural pneumonolyses over a seven-year period.

EXPLANATION OF TERMS

Complete pneumonolysis: All adhesions bearing any relationship to the diseased lung are severed or otherwise detached. The pneumonolysis is "*technically successful*" when this is accomplished.

Incomplete pneumonolysis: Some adhesions are severed but one or more remain. The pneumonolysis is "*technically unsuccessful*."

Partial pneumonolysis: An adhesion is partially divided.

Enucleation: The detaching of an adhesion from the parietal pleura in contrast with the usual method of severing. A section of parietal pleura is removed at the peripheral attachment of the adhesion.

Minor pneumonolysis: An operation attended with negligible risk of complications. Any thin adhesion, 2 cm. or more in length, can be safely severed. Many thicker and shorter adhesions can also be safely severed but the skill and experience of the surgeon are then determining factors. The same prevails in regard to small enucleations. The number of adhesions severed is relatively unimportant.

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Major pneumonolysis: An operation that may result in complications. Operations that fall within this classification are as follows.

1. Extensive enucleations.
2. Incomplete enucleations.
3. Partial division of adhesions.
4. Severing of certain types of adhesions, namely:
 - (a) Moderately thick adhesions less than 2 cm. in length (enucleation is safer).
 - (b) Short, thick cone-shaped adhesions (enucleation is safer).
 - (c) Complex bands in folds.

OPERATIVE PROCEDURE

In the series of operations here under consideration the two-puncture technique was used in all but a few of the earlier cases. Adhesions were routinely severed at the parietal pleura either with the galvanocautery or high-frequency current. The parietal pleura adjacent to the attachment of the adhesion was seldom anesthetized unless enucleation was contemplated.

Certain minor changes in technique have been made since the commencement of this series but the plan of procedure has remained the same in essentials. The patient's roentgenogram is conveniently available in the operating room illuminator. The patient is locally anesthetized, usually in the third or fourth intercostal space in the anterior axillary line. A sixteen-gauge needle is introduced and through it a long loosely fitting stilette; in this way the presence of an underlying adhesion can usually be detected and the distance of the lung from the chest wall estimated. A refill of air is given before the trochar and cannula are inserted in order to ensure adequate space for manipulation of the thoracoscope.

A complete inspection of the pleural space is made and operability of adhesions estimated. If these are readily operable they are severed. If they are not, the roentgenogram is studied to determine whether or not a major pneumonolysis is warranted. If pneumonolysis is decided upon, a second cannula is inserted in the most convenient intercostal space and through it is passed the instrument selected for the operation. The adhesions are then severed or enucleated. Bleeding areas, if any, are electrocoagulated. At the conclusion of the operation air is withdrawn until manometric pressures are moderately negative. The patient is then fluoroscoped in the upright position and, depending on the amount of collapse, air is added or withdrawn. A 30 per cent collapse is considered optimum for the average patient at this stage.

RESULTS OF 509 OPERATIONS 1936-1943

During an eight-year period pneumothorax was induced on 1,073 patients (table 1). Four hundred and fifty of these pneumothoraces were considered inadequate because of pleural adhesions and were inspected with the thoracoscope. Thus 41.8 per cent of patients with established pneumothoraces underwent thoracoscopy. Forty-nine patients did not have adhesions severed and the remaining 401 had 509 operations.

Of the 401 patients who had adhesions severed, 263 were far advanced, 121 moderately advanced and 17 minimal. Sputum was positive for tubercle bacilli in all but 25. There were 156 male and 245 female patients; 159 patients had pneumonolysis on the right side and 242 on the left; 83 patients had bilateral

pneumothorax; 31 had bilateral pneumonolysis. Nearly 2,000 adhesions were severed.

The average duration of pneumothorax before pneumonolysis was four months during the years 1936 to 1939. Since 1939 the interval before operation has gradually decreased and during the past few years has averaged slightly over four weeks. The majority of patients had only one operation but many had two or more. One of the bilateral pneumothorax patients had five operations on one side and one on the other.

All types of adhesions have been severed or otherwise detached from the parietal pleura. For a year or more at the beginning of this series of operations extreme caution prevailed in selection of adhesions for operation. There followed a period when many hazardous operations were undertaken and when, as seen in retrospect, the indications for pneumonolysis were sometimes exceeded. It was during this time that the majority of serious complications were encountered. It was at this time also that some of the most gratifying operative results occurred. This combination of serious complications and operative success with

TABLE 1
Thoracoscopy data 1936-1943

Total pneumothoraces induced.....	1,073
Total thoracoscopic examinations.....	567
Total patients examined (thoracoscopy).....	450
Ratio of thoracoscopy to pneumothorax.....	41.8 per cent
Thoracoscopy only (no operation).....	49
Thoracoscopy and pneumonolysis (patients).....	401
Thoracoscopy and pneumonolysis (operations).....	509

major pneumonolysis will be discussed later. It is pertinent to state here, however, that the risk of complications, even when an extensive operation is required, is more than justifiable provided that it is considered imperative to improve the pneumothorax. As a result of experience gained in what might be termed the periods of narrow and liberal indications, respectively, the plan of procedure to be discussed under "Indications and Contraindications" was evolved.

Evaluation of the clinical results of pneumonolysis is not always a simple matter, especially when the tuberculosis is bilateral. In this series, for example, 263 patients were classified preoperatively as far advanced, 83 had bilateral pneumothorax and 31 had bilateral pneumonolysis. Because of bilateral distribution it is evident that the success or failure of the operation cannot be decided on the basis of negative or positive sputum. The clinical results summarized in table 2 are based on radiological examination combined with sputum results in unilateral cases but frequently on radiological examination alone in bilateral cases. In unilateral cases a "clinically successful" result indicates cavity closure and diminution or contraction of infiltrated areas. This is determined in a postoperative interval of three or four months. In this interval

at least two consecutive concentrated sputum examinations must be negative. Technical results are determined at the conclusion of the operation and confirmed later by films. If all adhesions have been removed the operation is technically successful.

Pneumonolysis was considered technically successful in 289 of the 401 patients under consideration but of these only 253 had a clinically successful result; the remaining 36 patients were not benefited by the operation, even though a free collapse existed. Clinical failure in some instances was due to extensive involvement with an inadequate remaining amount of contractile lung tissue; in others it was due to blocked cavities. On the other hand, 52 patients classified as technically unsuccessful became clinically successful. Many of these so-called "technically unsuccessful" results could be more accurately described as "technically successful without complete pneumonolysis." Characteristic of this group is a patient with bilateral pneumothorax who had a complete pneumonolysis on one side and five operations including an extensive enucleation on the other. Following the final operation both pneumothoraces were free of adhesions

TABLE 2
Results of 509 operations on 401 patients

Technically and clinically successful.....	253 (63%)
Technically unsuccessful; clinically successful.....	52 (13%)
Total clinically successful....	305 (75%)
Technically successful; clinically unsuccessful.....	36 (9%)
Technically and clinically unsuccessful.....	60 (15%)
Total clinically unsuccessful.....	96 (24%)

radiologically and clinical success was abundantly clear. Because of one remaining inseparable mediastinal attachment this result falls in the technically unsuccessful class. The clinical success of this entire group of 52 patients whose pneumonolysis was incomplete indicates that any adhesions that remained were not sufficient to prevent an adequate, if not optimum, lung relaxation.

In contrast is the group of 60 patients with technically unsuccessful operations and clinically unsuccessful results. In some of these an adequate lung relaxation appeared to have been obtained. In the vast majority of this group of 60, however, it was inadequate in moderate or marked degree as manifested radiologically. It is interesting to note that there were more important complications with these patients than with all the remainder combined. That this should be so is not difficult to understand, for many major pneumonolyses were attempted, operations which sometimes offered only a slight hope of success. Although these more hazardous operations were usually undertaken when no alternative measure appeared indicated, yet in several instances attempts were made to release extensive adhesions when thoracoplasty would have been preferable. Extensive enucleations that required several operations fall in this category. Then, too, many adhesions were partially divided. In respect to these the partial division was at times electively undertaken but at others the impossibility

of complete division of an adhesion became evident only as the operation progressed.

It has already been stated that 31 patients underwent bilateral pneumonolysis. The results obtained reflect the value of pneumonolysis in a manner more marked than with the unilateral operation and for the reason that most of these patients were unsuited for any other form of treatment than bilateral pneumothorax. Twenty-three of the 30 patients had bilateral cavities and, probably without exception, were not good prospects for contralateral thoracoplasty, even though a successful unilateral pneumothorax was obtained. The remaining 8 patients had cavitation on one side only. Clinical success was achieved bilaterally in 21, unilaterally in 8 and on neither side in 2.

Results obtained by enucleation of adhesions have been included without special reference in the preceding paragraphs. Small enucleations require no further comment since these operations are of a relatively minor nature and are rarely associated with complications. More extensive enucleations are of considerable importance because such operations make it possible to remove otherwise inoperable adhesions and because serious complications are apt to occur. In this series of 501 operations, 50 moderate to extensive enucleations were attempted; 33 were completed and 17 were not. Clinically successful results were obtained in only 28, or 56 per cent. Empyema followed 6 operations (12 per cent). This contrasts with an empyema incidence of 2.5 per cent (13 patients) in the entire series. Extensive enucleations, complete and incomplete, accordingly accounted for nearly one-half of the important complications.

COMPLICATIONS

That thoracoscopy is a safe procedure is shown by the fact that complications were absent in the 49 patients who had this examination without severing of adhesions. Small transudates occurred in the costophrenic angle but in no case did this fluid reach the level of the dome of the diaphragm.

It is necessary to emphasize that many of the operations in this series exceeded the usual indications for pneumonolysis. It is also desirable to repeat that both the galvanocautery and electrosurgical methods were employed. The question of which of these methods is superior, especially in regard to complications, is one that I have not been able to determine with any finality. Nevertheless I am fully convinced that this is a relatively unimportant matter and that the question of complications depends chiefly upon the types of adhesions operated upon and, moreover, that this in turn is dependent upon the skill and experience of the operator.

The complications summarized in table 3 occurred during operation, immediately afterwards or within three months postoperatively. Mild emphysema and transudates in the costophrenic angle were common and in a liberal sense should not be regarded as true complications. Three patients had a marked degree of emphysema with its attendant discomfort, notably dysphagia, but in each case it was possible to preserve the pneumothorax. Pleural effusion in

moderate amount followed 22 operations within three days to four weeks but no massive effusion occurred. Ten patients either lost their pneumothorax or had it appreciably reduced in effectiveness because of adhesive pleuritis; in all but 3 this complication became apparent one month or more postoperatively.

In the table of complications "slight bleeding" indicates an amount of blood not exceeding 30 cc.; this as such should not be regarded as a true complication. In actual fact no record was kept of bleeding when this was in very small amount. The 20 cases of slight bleeding listed in table 3 averaged approximately 20 cc. but here also no accurate record was kept. It is sufficient to state that the amount and the effect of the bleeding were unimportant. The source of the bleeding was more commonly from trochar trauma than from the severed adhesions. "Moderate bleeding" as here under consideration indicates any quantity up to 500 cc.; it complicated 5 operations and each of these will be considered individually.

TABLE 3
Complications—509 operations on 401 patients

Mild (chest-wall) emphysema.....	common	Adhesive pleuritis.....	10
Severe (mediastinal) emphysema.....	3	Serous exudate (costophrenic	
Slight bleeding.....	20	angle).....	common
Moderate bleeding.....	5	Serous exudate (moderate).....	22
Severe bleeding.....	0	Serous exudate (massive).....	0
		Purulent exudate.....	13

Patient I had two moderate sized bands and five string adhesions completely severed with the galvanocautery. One remaining wide band in folds in the posterior apical area was partially severed with a resulting negligible amount of bleeding. Six hours later the patient was fluoroscoped because of symptoms of shock and an exudate in the lower third of the pleural space was observed. Thoracoscopy followed immediately and it was found that there was a steady dripping of blood from the parietal side of the partially severed adhesion. Superficial and deep electroagulation controlled the bleeding. Nearly 500 cc. of blood was then aspirated. Progress was uneventful thereafter.

Patient II had three moderate sized bands and five strings and cords severed with galvanocautery. The pneumonolysis was complete. Fluoroscopic examination fifteen hours later showed an exudate covering the dome of the diaphragm and approximately one inch above. Thoracoscopy established that bleeding had occurred at the site of a cannula puncture and that this had already ceased; 150 cc. of blood were aspirated.

Patient III also had a complete pneumonolysis; two bands were severed with the galvanocautery. One of these was thick and short, necessitating removal of an adjacent area of parietal pleura in order to avoid injury to the lung. During and after the release of the adhesion there was a little bleeding that was controlled without difficulty. Fluoroscopy immediately after operation showed a small exudate in the costophrenic angle. On the following morning the exudate had increased and covered the dome of the diaphragm. Six hours later there appeared to be no increase and thoracoscopy was not done. On the second postoperative day the amount of exudate was nearly doubled and tho-

racoscopy indicated that bleeding had recently occurred at the parietal stump of the adhesion that had bled during operation; 450 cc. of blood were aspirated. In the days following there was no further bleeding but the pneumothorax was allowed to become too small and an adhesive pleuritis subsequently resulted.

Patient IV had a network of small varicose veins at the parietal pleura where five string adhesions were attached. There were also seven bands of moderate size in the upper third posteriorly and anteriorly and one larger band in folds running from the medial apex to the costovertebral gutter; all but the latter were severed. Because of position of the cannulae and adhesions the string adhesions were the last to be reached. As the last of these was severed close to the parietal pleura there was a sudden steady spurt of blood from its parietal end. As a result the thoracoscope became fouled and a minute or two elapsed before adequate vision was obtained. By this time the bleeding had considerably subsided and only light superficial electrocoagulation was necessary; 150 cc. of blood were aspirated.

Patient V had a partial enucleation of a short folded band. The operation was technically difficult and should not have been undertaken. No second operation to complete the enucleation was contemplated. During the first postoperative night the patient coughed immoderately and on the following morning an exudate in the lower third of the pleural space was apparent by fluoroscopy. Thoracoscopic examination showed considerable oozing of blood at the point where cauterization had terminated on the previous day. This area was electrocoagulated and 300 cc. of blood were aspirated. The pneumothorax was electively terminated and thoracoplasty recommended.

In summary, then, moderate bleeding that complicated 5 operations was associated with the following:

1. Partial division of a complex adhesion.
2. Damage to intercostal vessel (cannula).
3. Complete enucleation of moderate extent.
4. Varicosity of parietal pleura.
5. Partial enucleation.

A less startling but undoubtedly a more serious complication of closed intrapleural pneumonolysis is empyema. Fortunately it is a complication that need seldom occur if the indications for pneumonolysis are not exceeded. In this series it complicated 13 out of 501 operations, but the incidence would have been appreciably less had there been more discrimination in rejection of patients for operation. As may be seen, by reference to table 4, that of 8 patients who developed tuberculous empyema 3 had a complete pneumonolysis.

Patient I was a young girl with far advanced bilateral disease, tuberculous enteritis and a preoperative temperature of 102°F.

Patient II was a middle-aged woman who had bilateral disease of an exudative character with cavitation on the operative side; she also had a preoperative temperature of 102°F. and tuberculous enteritis.

Patient III had unilateral involvement: two moderately sized cavities and infiltration of an exudative character. Preoperative temperature was 100°F. This patient might preferably have had thoracoplasty but pneumonolysis offered the only hope for the other 2.

Insomuch as all 3 patients had easily operable adhesions (minor pneumonolysis) it suggests that febrile patients with extensive disease and extrapulmonary complications are especially liable to pleural complications.

The remaining 5 patients who developed tuberculous empyema had incomplete pneumonolysis.

Patient IV was unsuitable for thoracoplasty because of the condition of the contralateral lung. He had a moderately sized cavity on the operative side with infiltration of a productive character scattered over half the lung. Clear fluid in variable amounts had been present since the induction of pneumothorax three months previously. The operation was of a minor nature.

TABLE 4
Complications—13 purulent exudates

	Pneumonolysis			TOTAL	
	Complete	Incomplete	Partial	Number	Per cent
Tuberculous empyema.....	3	2	3	8	1.5
Staphylococcal empyema.....	0	0	2	2	0.4
Mixed infection with bronchopleural fistula and spontaneous pneumothorax.....	0	0	3	3	0.6
Total.....	3	2	8	13	2.5

Patient V should have had thoracoplasty. She had previously had a tuberculous empyema which appeared to be well controlled with oleothorax. Four readily operable adhesions were severed leaving one apical band. The pneumothorax became effective insofar as the lung was concerned but the empyema returned. Subsequent thoracoplasty was fortunately successful.

The remaining three patients, (*VI*, *VII* and *VIII*) who developed this complication had incomplete pneumonolysis but in addition each had one adhesion partially severed. All were afebrile preoperatively. All were far advanced with cavitation.

Two patients developed staphylococcal empyema. *Patient IX* had unilateral involvement: a moderately sized cavity in the apical area and infiltration of an exudative character in the upper half. Her general condition was good and preoperative temperature normal. One extensive band was incompletely enucleated and it was planned to complete the operation within a few weeks. It was not conclusively established whether the pyogenic complication was from within or without but the former is more probable. Thoracoplasty would obviously have been preferable. *Patient X* was similar with the exception that thoracoplasty was contraindicated because of the condition of the contralateral lung.

The remaining three patients developed a mixed tuberculous-pyogenic infection. Each of these was far advanced with bilateral disease and each had a major partial pneumonolysis. It is presumed that in each case injury to lung caused a bronchopleural fistula. In *patients XI and XII* such a fistula was demonstrated by means of injection of methylene blue and *patient XIII* developed a spontaneous pneumothorax with gross manifestations of fistula.

In summary, tuberculous empyema followed 5 minor and 3 major pneumonolyses. Significant associated factors were as follows:

1. Preoperative fever; extrapulmonary complications.
2. Extensive exudative tuberculosis.
3. Concurrent pleural effusion.
4. Preëxisting tuberculous empyema, controlled by oleothorax.
5. Partial pneumonolysis.

Staphylococcal empyema complicated 2 major pneumonolyses and in each was associated with extensive incomplete enucleation.

Three mixed infections followed major incomplete (partial) operations.

INDICATIONS AND CONTRAINDICATIONS

Experience teaches that skill and judgement are of prime importance in an operation of this nature. Of these factors skill is more readily attained. Adequate judgment follows after several years of studying adhesions of all types and observing the effect of severing them; it also includes a sound knowledge of the treatment of tuberculosis in general and the capacity to select other forms of therapy in preference to pneumonolysis when this procedure is considered to be doubtfully beneficial or unduly hazardous. It should be accepted as an axiom that a difficult pneumonolysis, such as one involving an extensive enucleation, is acceptable only when alternate safer methods are considered inadequate. Restraint should be exercised with an ineffective pneumothorax of short duration; it may be preferable to delay a major pneumonolysis for a month or more, possibly supplementing the pneumothorax with a crushing of the phrenic nerve in the meantime. Again, there should be no hesitation in terminating a non-essential pneumothorax if thoroscopic examination indicates that a major pneumonolysis would be required to obtain an adequate relaxation. On the other hand, there need be no timidity about undertaking a major pneumonolysis if it is essential that a pneumothorax be maintained and improved, for even with such operations the incidence of complications is not unduly high. If a major pneumonolysis is undertaken, however, the surgeon should be reasonably sure that the operation can be completed; for not only is the partial division of an adhesion potentially hazardous but also the resultant effect on the pneumothorax is usually negligible.

In considering indications for pneumonolysis it must be remembered that the object of pneumothorax is the relaxation of a diseased lung and that an optimum relaxation cannot be obtained in the presence of restraining pleural adhesions. Such being the case it seems logical that all adhesions complicating

a pneumothorax should be severed regardless of whether or not clinical success appears to have been obtained. The fact that many pneumothoraces become effective even though adhesions are present does not refute the logic of this claim. The whole question of the adequacy of pneumothorax must be studied from a long range point of view. In this connection the observations of Hjalsted and Törning (1) are most interesting. In 1939 these Danish writers analyzed the results of 191 pneumothoraces five years after lung reëxpansion and concluded that results were twice as good in cases free from adhesions. More than twenty years ago Jacobaeus (2) arrived at a similar opinion.

Despite the desirability of adhesion-free pneumothorax this ideal is not always attainable. Moreover, under certain conditions it is not advisable to risk complications by attempting to rid a pneumothorax of adhesions. When, then, is pneumonolysis indicated and when contraindicated? The answer to this question hinges mainly on two factors: the extent and character of the tuberculosis and the extent and character of the adhesions. In the following summary the term major pneumonolysis indicates that the extent and character of the adhesions are such that important pleural complications may be expected, whereas the term minor pneumonolysis indicates a comparatively safe operation following which complications of importance are improbable.

1. In minimal tuberculosis minor pneumonolysis is indicated regardless of the effect already obtained by the pneumothorax; major pneumonolysis is not. If the adhesions interfere appreciably with free lung relaxation and are not readily operable it may be preferable to abandon the pneumothorax in favor of crushing of the phrenic nerve and bed-rest.

2. In moderately advanced tuberculosis, too, minor pneumonolysis is indicated regardless of the effect already obtained by the pneumothorax. If, however, adhesions are vertical and not easily operable it may be preferable to supplement the pneumothorax with hemidiaphragmatic paralysis rather than risk the complications of major pneumonolysis. Although major pneumonolysis is usually contraindicated in moderately advanced tuberculosis there is one notable exception and that is when the contralateral lung requires thoracoplasty. In such cases it is important to obtain a free relaxation of the ipsilateral lung as soon as possible even though this involves a major pneumonolysis.

3. Assuming that the indications for pneumothorax are not exceeded, minor pneumonolysis is usually indicated in far advanced tuberculosis. Occasionally, however, it is found that cavities become larger after induction of pneumothorax and in such cases it may be preferable to revise the treatment in favor of thoracoplasty. Major pneumonolysis is usually contraindicated if the contralateral lung is clear or nearly so; thoracoplasty is preferable, especially where there has been considerable lung destruction.

In far advanced tuberculosis with bilateral involvement and including both unilateral and bilateral pneumothorax, major pneumonolysis is frequently indicated. If thoracoplasty is contemplated on the contralateral side it is important to obtain an adequate pneumothorax as early as possible. To effect this, a major pneumonolysis is warranted. If bilaterally collapsed lungs require major

pneumonolysis to obtain a successful clinical result this should be done. It should be done because the end-results of bilateral pneumothorax are unsatisfactory unless a concentric bilateral collapse has been obtained. Finally, major pneumonolysis is indicated, if necessary, to convert an inadequate pneumothorax when thoracoplasty already exists on the contralateral side.

The absolute contraindications of pneumonolysis are febrile pleural effusion, tuberculous empyema and mixed tuberculous empyema. The presence of clear fluid is no contraindication, but if the effusion is recent or is accompanied by elevation of temperature it is desirable to postpone operation for at least one month after acute manifestations have subsided. In the presence of a progressive adhesive pleuritis pneumonolysis is usually contraindicated because of the impossibility of obtaining a free lung relaxation.

Other tuberculous complications do not contraindicate operation, but the likelihood of pleural reactions is probably increased when such extrapulmonary complications exist. The same may be said of the febrile patient and for this reason pneumonolysis, whether minor or major, should be delayed if temperature is 101°F. or more.

Finally, the partial division or the partial enucleation of an adhesion should be avoided. A partial pneumonolysis is usually permissible only when a second or third operation is planned to complete the release of the adhesion.

SUMMARY AND CONCLUSIONS

1. The indications and contraindications of closed intrapleural pneumonolysis have been described.

2. Conclusions reached are based on results of 509 operations on 401 patients. These results have been discussed. Particular attention has been given to complications.

3. With certain reservations, adhesions should be routinely severed within four weeks of the induction of pneumothorax in order to obtain an early and optimum lung relaxation.

4. Minor pneumonolysis (easily severed adhesions, small enucleations) is a procedure that is attended with little risk of complications.

5. Major pneumonolysis (complex adhesions, extensive enucleations) carries with it the danger of serious pleural complications. Nevertheless, if it is essential that a pneumothorax be maintained and improved, it is a warranted procedure.

6. Thoracoplasty is preferable to pneumothorax plus pneumonolysis where there is extensive lung destruction and a clear contralateral lung.

SUMARIO Y CONCLUSIONES

1. Describense las indicaciones y contraindicaciones de la neumonolisis intrapleural cerrada, basándose las conclusiones en el resultado de 509 operaciones en 401 enfermos y dedicándose atención cuidadosa a las complicaciones.

2. Con ciertas reservas deben resecarse sistemáticamente las adherencias en

término de cuatro semanas del establecimiento del neumotórax, a fin de obtener una dilatación pulmonar temprana y óptima.

3. La neumonolisis menor (adherencias fáciles de desprender, enucleaciones pequeñas) constituye un procedimiento que entraña poco peligro de complicaciones.

4. La neumonolisis mayor (adherencias complejas, enucleaciones extensas) entraña el peligro de producir complicaciones pleurales graves, pero está justificada si es indispensable mantener y mejorar un neumotórax.

5. Cuando hay extensa destrucción pulmonar y un pulmón contralateral despejado, la toracoplastia es preferible al neumotórax más la neumonolisis.

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DIAPHRAGMATIC PARALYSIS AND PNEUMOPERITONEUM¹

Therapeutic Observations in White Patients

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We have used the combination of temporary phrenic nerve interruption and pneumoperitoneum in the treatment of 546 white patients with reinfection type pulmonary tuberculosis. There have been 23,823 refills.

Every effort has been made to exclude patients with nontuberculous disease from this series. The time lag, which averaged several weeks between the X-ray film on application of the patient and his Sanatorium admission, has been of considerable help in ruling out acute nontuberculous conditions. It is particularly believed that no case of lung abscess, bronchiectasis, virus pneumonia, fungus disease, silicosis, bullous emphysema, sarcoid or neoplasm has been included. Patients with these conditions are constantly admitted to the Sanatorium for study and diagnosis, and all such have been carefully excluded. Tubercle bacilli have been found in every case that had cavity demonstrable by X-ray.

All cases in this series with negative sputum were positive to 0.1 mg. of Old Tuberculin, and all but 5 of these had intimate contact with known open cases of pulmonary tuberculosis. A Fontana stain and a culture on Sabouraud's media were done routinely in all sputum-negative patients. If direct sputum smears were negative for tubercle bacilli, three concentrations were done. If these were negative, culture and guinea pig inoculation followed. In every case in which a satisfactory sputum specimen was not obtainable, a culture or guinea pig inoculation of the concentrated gastric contents was done.

In evaluating the statistical data it is important to bear in mind that the majority of the cases in this series had far advanced tuberculosis and that many had either a poor or extremely poor prognosis. Table 1 shows that, of the total number of 546 patients, 349, or 63.9 per cent, were far advanced; 188, or 34.4 per cent, were moderately advanced and 9, or 1.6 per cent, were minimal. The prognosis was considered from poor to extremely poor in 321, or 58.7 per cent; questionable in 163, or 29.8 per cent; and good in 62, or 11.3 per cent. One hundred and thirty patients, or 23.8 per cent, had one or more serious tuberculous complications when the collapse treatment was begun. Eighty-seven, or 15.9 per cent, had thick-walled cavities and an excessive amount of fibrosis. Pneumothorax was tried first and found either impossible or unsatisfactory in 175 of the patients; in some of these a mechanically satisfactory collapse could have been obtained had inadvisable extensive pneumonolysis operations been done.

In addition to the 546 cases, our records show that pneumoperitoneum was started in 27 other patients who received only a few refills after its induction. These 27 patients were not considered in our statistical study because they

¹ From the Georgia State Tuberculosis Sanatorium, Alto, Georgia.

definitely did not give pneumoperitoneum anything like a fair trial. Twenty-one of this group left the Sanatorium against medical advice soon after pneumoperitoneum was started. The other 6 were of the extremely nervous type and for various reasons felt that they could not continue refills.

The factors chosen for evaluating this form of treatment were the classification of disease, the observation time, the number of cavity closures and sputum

TABLE 1

What has happened to the 546 cases who have or have had treatment with phrenic nerve interruption and pneumoperitoneum

CLASSIFICATION	NUMBER OF CASES	TREATMENT DISCONTINUED AS UNSATISFACTORY	TREATMENT DISCONTINUED FOR THORACOPLASTY	UNACCOUNTED FOR (NO CONTACT)	DEAD	TREATMENT TERMINATED AS APPARENTLY SUCCESSFUL	STILL UNDER TREATMENT
Minimal.....	9	0	0	0	0	0	9
Moderately advanced....	188	3	0	0	1	44	140
Far advanced.....	349	16	17	18	77	30	191
Total.....	546	19	17	18	78	74*	340

* Cavities have reopened in 2 of these cases. See table 7.

TABLE 2

The number of positive and negative sputa and the number and percentage of sputum conversions, according to classification, in the entire series of 546 cases treated with phrenic nerve interruption and pneumoperitoneum

CLASSIFICATION	NUMBER OF CASES	SPUTUM BEFORE TREATMENT		NUMBER OF CONVERSIONS	PER CENT OF CONVERSIONS
		Positive	Negative		
Minimal.....	9	0	9	0	0
Moderately advanced.....	188	116	72	97	83.6
Far advanced.....	349	349	0	168	48.13
Total.....	546	465	81	265	56.9

conversions, the number showing either marked retrogression or complete disappearance of exudative lesions, and the incidence of complications.

It is shown in table 2 that 465, or 85 per cent, of the total number of patients had a positive sputum at the time treatment by phrenic paralysis and pneumoperitoneum was instituted. It may seem as if the remaining percentage of 14.8 with negative sputum is rather high when only 9, or 1.6 per cent, are classified as minimal. However, there is some latitude as to what lesions may properly be classified as minimal and what as moderately advanced. Our cases classified

as minimal have not only been made to meet the total extent limitation, but also possibly a somewhat restricted opinion as to what constitutes slight lesions. National Tuberculosis Association Standards as to classification and clinical status have been used throughout this article.

Four hundred and fifty-six patients, or 83.5 per cent, had demonstrable pulmonary cavitation when treatment was begun. Of the 456 with cavitation, 331, or 72.5 per cent, had excavation in one lung; 125, or 27 per cent, had one or more cavities in each lung. Simultaneous bilateral phrenic paralysis was done in no case, but in 30 instances the nerve on the opposite side was crushed after regeneration of the nerve first interrupted had taken place. In 59 cases the cavity size was 2.5 cm. or less; in 141 the cavity diameter was 2.5 to 4 cm.; 256 patients had cavities which ranged in diameter from 4 to 12 cm. All roentgenograms were made with a tube distance of 6 feet.

In the follow-up study for evaluation of this therapy, it was found that 18 of the total number of 546 cases could not be traced. This leaves 528 who were traced, and 436 of these had cavitation at the time the collapse treatment was started. In these 436 cases with excavation, in whom phrenic paralysis and pneumoperitoneum is either being continued or has been terminated, 276, or 63.3 per cent, show apparent closure of all cavities; in 160, or 36.6 per cent, roentgenograms show that all cavities are not closed. It was found that closure of cavities in the base occurred only 5 per cent more frequently than in the apex and only 1 per cent more frequently in the middle third than in the apex. Taking into consideration that, as usual, more thick-walled cavities were present in the apex than elsewhere, it seemed that cavities of comparable character closed just as readily in the apex as in any other part of the lung. Of the 528 cases who were traced, 120 show definite clearing of the infiltrative shadows; 207 show marked clearing and 69 have had a complete disappearance of abnormal shadows. In 22 patients the X-ray appearance is unchanged and in 32 the lesions are now progressive. Seventy-three of the 78 patients who died had progressive pulmonary lesions.

Table 1 is an abbreviated presentation of what has occurred in the 546 cases who had phrenic nerve interruption and who, except the 18 cases unaccounted for, have given or are giving pneumoperitoneum a fair trial. This table shows that pneumoperitoneum was discontinued as unsatisfactory in 19 cases. Six of these 19 had extensive productive lesions, 4 had considerable abdominal pain, apparently due to subdiaphragmatic adhesions, and 9 were discontinued in order to have a trial of pneumothorax. Although the collapse was considered unsatisfactory in all 19 cases, 13 showed improvement at the time pneumoperitoneum was discontinued, while 6 were unimproved.

In the group of 78 dead, one patient had quiescent disease and died by suicide. Two died of tuberculous meningitis; in one of these the pulmonary condition was unimproved, but the other showed 50 per cent clearing of the infiltrative shadows and apparent closure of a 4 cm. cavity within six weeks after the collapse was begun. One patient who had a 5 cm. cavity in the hilum, which was reduced to 2 cm. in diameter in eight weeks, died suddenly of pulmonary

hemorrhage. Another patient who had a 10 cm. tension cavity died suddenly of pulmonary hemorrhage after the cavity had shrunk to only 1 cm. in diameter; this patient had a Monaldi procedure in conjunction with phrenic paralysis and pneumoperitoneum. Two of the 3 patients who had severe silicosis as a complication are dead and the other is worse. One patient died of carcinoma of the uterus.

TABLE 3

Nine minimal cases still under treatment with phrenic nerve interruption and pneumoperitoneum

OBSERVATION TIME UNDER TREATMENT	NUMBER OF CASES	SPUTUM BEFORE TREATMENT		PRESENT CLINICAL STATUS			
		Positive	Negative	Apparently arrested	Quiescent	Improved	Unimproved
2 to 3 months.....	3	0	3	0	0	2	1
3 to 6 months.....	5	0	5	0	4	1	0
6 to 12 months.....	1	0	1	1	0	0	0
Total.....	9	0	9	1	4	3	1

TABLE 4

One hundred and forty moderately advanced cases still under treatment with phrenic nerve interruption and pneumoperitoneum

OBSERVATION TIME UNDER TREATMENT	NUMBER OF CASES	SPUTUM BEFORE TREATMENT		NUMBER CONVERTED	PER CENT	PRESENT CLINICAL STATUS			
		Positive	Negative			Apparently arrested	Quiescent	Improved	Unimproved
2 to 3 months.....	35	21	14	15	71.4	0	0	20	15
3 to 6 months.....	14	4	10	4	100.0	0	8	4	2
6 to 12 months.....	31	21	10	16	76.0	0	26	3	2
12 to 18 months.....	21	21	0	17	80.9	9	10	1	1
18 to 24 months.....	22	14	8	13	92.8	20	1	1	0
24 to 30 months.....	17	9	8	7	77.7	15	1	1	0
Total.....	140	90	50	72	80.0	44	46	30	20

It is realized that the time element is very important in evaluating any form of pulmonary collapse, and in this connection one may question the justification for including in tables 4 and 5 the two groups who have had treatment from two to three months and from three to six months, respectively. The percentage of sputum conversions in these groups seems to be sufficient grounds to warrant their inclusion; however, the percentage of conversions in these groups does not and cannot represent either the average or the actual length of time required to effect a conversion in the other cases. It will be seen in these same tables that the number and percentage of conversions are placed opposite or on the

same line as "Observation Time under Treatment." This does not necessarily mean that the time required for sputum conversion is the same as the "Observation Time under Treatment." Our records show that 70 per cent of the sputum-positive patients that ultimately became negative did so within the first six months of treatment. For instance, table 5 shows that 13 cases, or 44.8 per cent, of the 29 sputum-positive cases who have had treatment only two to three months have become negative. These 13 conversions may well represent 70 per cent of all that will ultimately become negative in this group.

The total number and percentage of sputum conversions in the 465 sputum-positive cases shown in table 2 may at first give the impression of poor results. But when it is remembered, as stated above, that 349 patients (table 1) were

TABLE 5

One hundred and ninety-one far advanced cases still under treatment with phrenic nerve interruption and pneumoperitoneum

OBSERVATION TIME UNDER TREATMENT	NUMBER OF CASES	SPUTUM BEFORE TREATMENT		NUMBER CONVERTED	PER CENT	PRESENT CLINICAL STATUS				
		Positive	Negative			Arrested	Apparently arrested	Quiescent	Improved	Unimproved
2 to 3 months.....	29	29	0	13	44.8	0	0	6	18	5
3 to 6 months.....	16	16	0	8	50.0	0	0	12	4	0
6 to 12 months.....	38	38	0	26	68.4	0	0	32	5	1
12 to 18 months.....	30	30	0	27	90.0	0	0	30	0	0
18 to 24 months.....	21	21	0	21	100.0	0	0	18	3	0
24 to 30 months.....	21	21	0	18	85.7	0	15	2	4	0
30 to 36 months.....	27	27	0	22	81.4	2	21	3	0	1
3 to 4 years.....	8	8	0	5	62.5	0	5	2	0	1
4 to 5 years.....	1	1	0	0	0	0	0	1	0	0
Total.....	191	191	0	140	73.2	2	41	106	34	8

far advanced and that 321 had either a poor or extremely poor prognosis, the conversion rate is much better than we had expected.

Of the 30 far advanced cases in whom treatment was terminated as apparently satisfactory (table 7), the cavity reopened in 2. In this connection it is readily conceded that the cavity or cavities may reopen or new areas of infiltration may occur in some of the other cases, particularly in those who have been under observation only a few months. But so far, the other 28 far advanced cases, as well as the 44 moderately advanced cases shown in table 6, have continued to do well. The collapse treatment has not been terminated in any of the 9 patients with minimal tuberculosis.

We have not found the procedure of pneumoperitoneum a formidable one. The following are the essentials of the procedure of initiating pneumoperitoneum and giving refills. Sterilize the skin in the usual way. Use the same needles employed in giving artificial pneumothorax. Anesthetize a needle tract in the abdominal wall; a site about two or three inches below the left costal margin

and just lateral to the border of the rectus muscle has usually been found satisfactory. Introduce the point of the larger needle into the peritoneal cavity; the hollow abdominal viscera are not easily punctured, even with sharp needles. Pull back the syringe plunger in order to be sure the needle is not in a blood vessel. With light pressure on the plunger introduce 2 or 3 cc. of air; if this goes in easily and freely, connect the needle with the pneumothorax apparatus.

TABLE 6

Forty-four moderately advanced cases in whom collapse treatment has been terminated as apparently satisfactory

LENGTH OF OBSERVATION TIME SINCE TERMINATION OF PNEUMOPERITONEUM	NUMBER OF CASES	SPUTUM				PRESENT CLINICAL STATUS		
		Before treatment		Converted during treatment	Still negative	Appar- ently cured	Arrested	Appar- ently arrested
		Positive	Negative					
6 months....	4	2	2	2	4	0	0	4
6 to 12 months....	12	8	4	8	12	0	2	10
12 to 18 months....	9	3	6	3	9	0	7	2
18 to 24 months....	17	11	6	11	17	12	5	0
27 months....	1	1	0	1	1	1	0	0
3 years.....	1	0	1	0	1	1	0	0
Total.....	44	25	19	25	44	14	14	16

TABLE 7

Thirty far advanced cases in whom collapse treatment was terminated as apparently satisfactory

LENGTH OF OBSERVATION TIME SINCE TERMINATION OF PNEU- MOPERITONEUM	NUM- BER OF CASES	SPUTUM					PRESENT CLINICAL STATUS		
		Before treatment		Con- verted during treat- ment	At present		Appar- ently cured	Ar- rested	Quies- cent
		Posi- tive	Nega- tive		Again posi- tive	Still nega- tive			
6 to 8 months.....	2	2	0	2	2	0	0	0	2
1 to 2 years.....	14	14	0	14	0	14	1	13	0
2 to 2½ years.....	12	12	0	12	0	12	8	4	0
2½ to 3 years.....	2	2	0	2	0	2	2	0	0
Total.....	30	30	0	30	2*	28	11	17	2

* Cavities have reopened in these 2 cases.

Open and immediately close the stopcock which controls the air flow. If the air is not going in freely there will be an excessively high positive manometric reading and probably pain. If these are not present the introduction of air may be continued. Fluctuations of the manometer are not so readily obtained in pneumoperitoneum as in pneumothorax, but neither are they so necessary. The principal objective, of course, is that the air freely enters the peritoneal cavity, and this is known by the absence of an excessively high manometric reading. Unnecessary lengths of time need not be consumed in attempts to

obtain free fluctuations since it is possible without them to know that air is freely entering the peritoneal cavity.

The procedure of initiating pneumoperitoneum and giving refills is believed to be much less dangerous, and certainly is more readily learned, than is that of pneumothorax. At present, when excessive collapse is avoided and selective and bilateral pneumothorax are common, considerable care has to be exercised with refills in order not to perforate the lung. Pneumoperitoneum of course should not be done without due care, but with only a moderate amount of familiarity with the method it can be done as rapidly and more confidently than pneumothorax. Serious accidents undoubtedly could occur as the result of ineptness in attempts to introduce air into the peritoneal cavity, but such accidents should be considered in the same light as the many which have occurred for the same reason in giving pneumothorax. Since pneumoperitoneum refills require larger amounts of air, usually about 800 to 1,000 cc. a week, the performance is considerably facilitated if the proper bottle of the pneumothorax apparatus is elevated to about the limit of the height of an ordinary irrigation stand.

Pneumoperitoneum should be as diligently given and as persistently followed as is done in either pneumothorax refills or a series of thoracoplasty operations. It is our belief that, to expect full benefit, the paralyzed half of the diaphragm should be elevated, if possible, to about the level of the third anterior interspace, and kept there throughout treatment. However, many respond satisfactorily with less elevation while some may require more. Extensive subdiaphragmatic adhesions may so greatly limit the rise of the diaphragm that pneumoperitoneum is ineffectual.

Pneumoperitoneum has not been found to cause any more discomfort, in either bed or ambulatory patients, than artificial pneumothorax. We do not feel sure of its value, but practically all of our patients have worn an abdominal supporter. In order to avoid a slight feeling of emptiness in the abdomen as air is absorbed between refills, patients will gradually tighten the belt; this practice may be of some value in maintaining a more or less constant intra-abdominal pressure. The use of a supporter is desirable from an esthetic standpoint.

From our experience we believe that pneumoperitoneum should be established, if possible, before the phrenic nerve is interrupted. This order of procedure enables one to determine, first of all, whether the establishment of pneumoperitoneum is possible and whether there is likely to be a satisfactory rise of the diaphragm. Subdiaphragmatic adhesions, and even the evidence of basal pleural adhesions, can be revealed by inflating the peritoneal sac. Either one or both of these conditions may prevent a satisfactory pneumoperitoneum by a poor rise of one or both halves of the diaphragm. If it is decided that a satisfactory rise of the diaphragm is not going to be attained, and if another form of collapse is contemplated, especially thoracoplasty, an interrupted phrenic nerve would not be desirable. In patients with lesions of like character and equal extent in each lung, there is often some doubt as to which half of the

diaphragm should be paralyzed. Because of the information pneumoperitoneum reveals in regard to adhesions, better results will frequently be obtained in such cases if the decision as to which phrenic nerve should be interrupted is postponed until after the pneumoperitoneum is established.

Special pains should be taken in crushing the phrenic nerve in order that the resulting paralysis may be temporary and not permanent. At this time, permanent paralysis has apparently occurred in 5 per cent of the cases presented in this series. Because of the smaller amount of trauma and scar tissue formation, we are of the opinion that there is less likelihood of permanent paralysis if a short longitudinal slit is made in the nerve sheath and only the nerve is lifted up and crushed or cut in two, rather than if both the sheath and nerve are crushed.

One of our chief reasons for using phrenic paralysis and pneumoperitoneum in cases that formerly would have been considered ideal for pneumothorax, and in many instances where thoracoplasty seemed to be the only choice of treatment left, is the extremely low incidence of complications. The only serious complication we have seen has been tuberculous peritonitis with ascites. This occurred in 5 patients, or 0.9 per cent. One recovered and 4 who had this complication died. Whether or not the further use of pneumoperitoneum will show that the low incidence of this serious complication will continue is our chief concern, as it seems to us that it is on the incidence of this complication that a final evaluation of this form of collapse treatment will be determined. There have been no deaths, accidental or otherwise, resulting from the procedure of pneumoperitoneum. Less than 2 per cent developed an emphysematous type of inguinal herniation. In every case the hernia was reduced, a truss fitted and treatment continued. Because of the possibility of this complication, it is advisable to have a truss adjusted on all prospective pneumoperitoneum patients who have a definitely relaxed ring. Pneumoperitoneum is not necessarily contraindicated in ruptured patients, but of course a truss should be properly fitted before treatment is started.

Our experience has led us to believe that phrenic nerve interruption and pneumoperitoneum can be effective in a much larger number of patients than any other one method of collapse therapy. This statement calls for some appraisal of artificial pneumothorax. We have employed pneumothorax in treating 2,784 patients. All known procedures for obtaining a satisfactory collapse, such as pneumonolysis, have been readily available, as have all other collapse measures. One patient died suddenly of air embolism as the result of a refill. There has been no other immediate or early death from an accidental cause. Our patients with pneumothorax have had the usual number of more or less serious late complications. The serious late complications and sequelae encountered in the treatment of tuberculosis with pneumothorax have entailed a vast amount of work in trying to cure the complication or to prepare the patient for some other form of collapse therapy. Such rather formidable procedures as aspiration, irrigation, oxygen lavage, open drainage, tidal irrigation, oleothorax and thoracoplasty have not always provided the answer for an

unexpandable lung, bronchopleural fistula and empyema with great pleural thickening.

It is clearly evident that pneumothorax has been widely misused and improperly managed, but all of the difficulties encountered cannot be attributed to its haphazard use. The reasons why the results have been unsatisfactory in a large percentage of patients are now generally known. There are adequate grounds for some difference of opinion as to what constitutes the misuse of pneumothorax, but any collapse therapy that is either satisfactory in only a very limited number of patients, or is so frequently followed by serious complications when used in patients with more extensive disease, certainly leaves a great need for some other form of temporary collapse. We believe that, if the combination of phrenic nerve interruption and pneumoperitoneum is a part of the collapse treatment, the necessity for making many difficult and questionable decisions in regard to the use of pneumothorax will be avoided.

Many recoveries have occurred as a result of permanent phrenic paralysis, since avulsion of the nerve frequently resulted in sufficient immobility and pulmonary collapse. However, we abandoned this type of treatment ten years ago because there was a permanent loss of too much lung volume, and other forms of treatment, later found to be indicated in some patients, were impossible. Phrenic nerve interruption has been employed by us in 1,915 patients with benefit to many, but too often a temporary phrenic nerve interruption alone gives neither enough collapse nor limitation of motion. This also is true of pneumoperitoneum, and it is our opinion that only rarely is either procedure alone justified.

Since learning to give due attention to essential preoperative and postoperative details and not removing too many ribs at one operation, thoracoplasty is now performed with low operative mortality. It is sufficiently safe that there is no hesitancy in employing it when indicated; of course some cavities cannot be closed by this method regardless of the amount of bone removed, and in practically every case important amounts of functioning lung are permanently collapsed. The limitations of other forms of treatment of pulmonary tuberculosis are generally conceded. The indications, contraindications and management of pneumothorax and thoracoplasty are now reasonably well understood and we still find a tremendous number of patients who are not suitable for either of these forms of treatment. Our experience with temporary phrenic nerve interruption and pneumoperitoneum has led us to the conclusion that this method is capable of effecting a cure in a large percentage of these patients who unquestionably are not suitable either for pneumothorax or for thoracoplasty, and that it will make suitable for thoracoplasty a considerable number not likely to become so without some form of preliminary collapse.

When artificial pneumothorax has been decided upon as the treatment of choice but is found to be impossible or inadvisable on account of adhesions, we are of the definite opinion that thoracoplasty should not be resorted to immediately. That is, of course, provided that the lesions are largely exudative and that cavities have thin or moderately thin walls. The use of phrenic nerve inter-

ruption and pneumoperitoneum will effect a complete cure in many such patients without the necessity of resorting to thoracoplasty.

In the absence of extensive fibrosis, thin or moderately thin walled cavities not favorably influenced by phrenic nerve interruption and pneumoperitoneum are strong presumptive evidence that they are of the tension type. Prolonged continuation of pneumoperitoneum, in the hope that tension cavities will eventually close, is usually useless. Our experience in the use of the Monaldi procedure in conjunction with pneumoperitoneum is limited, but we believe it is often preferable, particularly in patients with large tension cavities and extensive exudative lesions, to continue pneumoperitoneum in conjunction with a Monaldi procedure, rather than to abandon it and perform thoracoplasty. Even large, thick-walled tension cavities can, at least, be reduced in size by use of the Monaldi procedure and pneumoperitoneum, provided there is a sufficient amount of reasonably elastic adjacent lung tissue. If a thoracoplasty eventually is required it likely will be much less extensive than if it had been done in the first place.

Knowing some of the reasons for the beneficial effects of collapse in the treatment of pulmonary tuberculosis, it seems logical that temporary phrenic nerve interruption and pneumoperitoneum would be of value. In the first place the amount of reduction of lung volume that can easily be obtained with this method is as great as that usually desired in pneumothorax. The most casual comparison, by fluoroscopic examination, of patients with pneumothorax with those who have phrenic nerve interruption and pneumoperitoneum will show that those with pneumothorax have a tremendously larger amount of respiratory motion. Of course, pneumothorax patients with excessive collapse or greatly thickened pleurae have little if any respiratory motion, but the possible consequences of such conditions take them out of the satisfactory group. In the presence of phrenic paralysis and pneumoperitoneum, the paralyzed half of the diaphragm will be seen to be practically if not entirely immobile. The lung is compressed into the upper portion of the thoracic cage where there is very little costal movement. The basic factors of reduction of lung volume and limitation of respiratory motion are accomplished without the separation of the lung from any of its protective surrounding structures; and the complications due to air in the peritoneal cavity in no way are comparable in frequency, and extremely rarely in seriousness, with those encountered with air in the pleural cavity.

It is an easy matter to follow the progression or the retrogression of lesions as revealed by serial X-ray films in patients on bed-rest alone. But during the course of treatment with pneumothorax or after a thoracoplasty has been done the X-ray film does not reveal so clearly what is taking place in previously known areas of disease. It is true that one usually can determine when cavities are closed and areas of infiltration are well collapsed, but it is difficult if not impossible to determine by X-ray films when healing has taken place. On the other hand, the X-ray film reveals lesions and their changes, if any, during the period of collapse with pneumoperitoneum just as clearly as it did before treatment was started. This is accounted for by the fact that atelectatic areas are

rarely seen and the lung has the appearance of being well ventilated. Being able to see almost if not exactly what is taking place in the lung during the period of collapse is of tremendous value in deciding when treatment can safely be terminated. Incidentally, it seems that pneumoperitoneum may be terminated as rapidly as is desired. In most of our patients in whom it has been terminated, refills were simply discontinued and no undesirable effects have been observed.

Following the termination of collapse there is believed to be a maximum, or at least a satisfactory, restoration of original lung volume and function. There is either a minimum or no permanent loss of good lung tissue provided a permanent paralysis of the hemidiaphragm is avoided. There is no evidence, either from physical or X-ray examination, that the patient has ever had collapse therapy at all. The belief that maximum lung volume and function are restored after treatment has been discontinued is based only on the appearance of the roentgenogram. The X-ray films show the diaphragm back in approximately the same position as before treatment; they show no unexpandable lung, no contraction of the bony framework of the chest, no distortion or displacement of the mediastinal structures, no thickened pleurae and no small or greatly contracted lung.

The most important criterium by which the value of any collapse therapy is judged is by its ability to close cavities and convert sputum, and to do so with the least likelihood of serious complications or sequelae, and with the maximum conservation of normal lung tissue. These are the criteria upon which we have chiefly based our present appraisal of temporary phrenic paralysis and pneumoperitoneum in the treatment of pulmonary tuberculosis. We have been forced to the conclusion that, unless further experience reveals some results not heretofore seen, the wide-spread proper use of temporary phrenic nerve interruption and pneumoperitoneum will mark a much greater advance in the treatment of pulmonary tuberculosis than did the beginning of the extensive employment of artificial pneumothorax.

SUMMARY AND CONCLUSIONS

The results in treating 546 patients with pulmonary tuberculosis by the combination of temporary phrenic nerve interruption and pneumoperitoneum have been presented. The technique of the procedure of pneumoperitoneum has been outlined. The complications encountered have been enumerated. The advantages of phrenic paralysis and pneumoperitoneum, as compared with other forms of collapse therapy, have been discussed.

Although the prognosis in this series was poor or extremely poor in 58.7 per cent, questionable in 29.8 per cent and good in only 11.3 per cent, apparent closure of all cavities has been attained in 63.3 per cent of the cases and conversion of the sputum has occurred in 56.9 per cent. Serious complications have been infrequent.

The combination of temporary phrenic nerve interruption and pneumoperitoneum apparently is a reasonably satisfactory method of collapse in patients with pulmonary tuberculosis of all classifications, provided the lesions are not

old and rigid. However, in some patients who have both productive and exudative lesions, the method is of value as a preparatory treatment for thoracoplasty.

A fairly large number of patients who ordinarily would have a thoracoplasty, with the consequent permanent loss of important amounts of functioning lung, can be cured by phrenic paralysis and pneumoperitoneum without sacrificing practically any normal lung tissue.

Satisfactory results can be obtained by the use of phrenic paralysis and pneumoperitoneum in a considerable number of patients with most extensive exudative lesions and pleural adhesions, and in whom no other collapse measure is possible or indicated, and in whom bed-rest or any other form of therapy would in all probability be inadequate.

The employment of phrenic paralysis and pneumoperitoneum makes it possible to confine the use of artificial pneumothorax to those patients with very limited lesions and with few if any adhesions, and without denying the benefits of temporary collapse therapy to those with more wide-spread involvement of the lungs and extensive adhesions.

SUMARIO Y CONCLUSIONES

En este trabajo expónese el resultado obtenido en 546 tuberculosos pulmonares tratados mediante la combinación de la interrupción temporal del frénico y el neumoperitoneo, describiéndose la técnica de este último procedimiento y las complicaciones observadas. También se comparan las ventajas de la parálisis del frénico y del neumoperitoneo con las de otras formas de colapsoterapia.

Aunque el pronóstico en esta serie era sumamente malo en 58.7%, dudoso en 29.8% y bueno en sólo 11.3%, obtúvose cierre aparente de todas las cavernas en 63.3% de los casos y conversión del esputo en 56.9%. Las complicaciones graves fueron raras.

La combinación de la interrupción temporal del frénico y del neumoperitoneo representa aparentemente un medio razonablemente satisfactorio para obtener el colapso en los tuberculosos pulmonares de todas clases, con tal que las lesiones no sean antiguas y rígidas. Sin embargo en algunos enfermos que muestran lesiones tanto húmedas como exudativas, la técnica resulta de valor como tratamiento preparatorio para la toracoplastia.

Un número bastante crecido de enfermos en los que se haría habitualmente una toracoplastia, con la consiguiente pérdida permanente de porciones importantes de pulmón funcionante, puede curarse por medio de la parálisis del frénico y del neumoperitoneo sin apenas sacrificar tejido pulmonar normal.

Mediante el empleo de la parálisis del frénico y del neumoperitoneo pueden obtenerse resultados satisfactorios en un número considerable de enfermos que muestran lesiones exudativas y adherencias pleurales muy extensas, y en los que no es posible ni está indicada otra medida de colapso y en los que el reposo en cama u otra terapéutica resultaría con toda probabilidad inadecuado.

El empleo de la parálisis del frénico y del neumoperitoneo permite restringir el empleo del neumotórax terapéutico a los enfermos con lesiones limitadísimas

sin excluir del beneficio de la colapsoterapia temporal a los que muestran invasión más difusa de los pulmones y extensas adherencias.

Note: In the elimination of nontuberculous disease we are indebted to Dr. David T. Smith of Duke University for generous assistance in the confirmation and identification of fungus organisms. Dr. Robert C. Major of the University of Georgia School of Medicine has been of invaluable aid by doing the indicated bronchoscopic work.

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PNEUMOPERITONEUM AND DIAPHRAGMATIC PARALYSIS¹

Therapeutic Observations in 110 Negroes

NORMAN LARUE ANDERSON² AND WILLIAM DOUGLAS WINN

INTRODUCTION

The history of pneumoperitoneum and phrenic nerve crush as a treatment of pulmonary tuberculosis has been adequately covered in earlier publications by various authors. In some institutions this form of therapy has been accepted as a useful procedure in the treatment of tuberculosis. In other institutions pneumoperitoneum is not regarded as worth while, except in a very limited number of cases. Because we³ feel that this form of therapy has such a definite indication in the treatment of a large number of tuberculous patients, and since it appears that it is not being used to full extent throughout the country, we are recommending its further use in properly selected cases.

It has been our feeling that one of the reasons that many doctors throughout the country are opposed to pneumoperitoneum as a therapeutic approach to tuberculosis is that they have not tried it themselves in a sufficient number of cases. Another very important reason is the failure to recognize that both hemidiaphragms must be pushed upward to the point of tolerance of the patient. Unless a maximum dose of air is given, a maximum response to therapy cannot be expected. It has been perfectly obvious in some of our cases that maximum response has not been attained, since, when refills of air are increased, the lung disease responds more favorably than previously. Unlike artificial pneumothorax this therapy must first overcome the resistance of the diaphragm before lung volume can be decreased.

Several physicians have visited this institution in the past three years. Almost invariably they are initially skeptical about the use of pneumoperitoneum and phrenic nerve crush in the treatment of tuberculosis. Most of these physicians have looked through our files of X-ray films and seen the patients receiving this form of therapy. Not one has gone away without being enthusiastic over the apparent good results which are being obtained.

In a previous report, Crow (1) has covered the results of pneumoperitoneum and phrenic nerve crush in 154 white patients receiving this form of treatment in this institution. Our report seeks to cover the results of the same treatment in all colored patients here. The results have been remarkably similar and we feel that there is appreciably no significant variation in response to this type of therapy in the white and colored races. The striking results at this institution have already been heralded by such a seasoned thoracic physician as Holmes who

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³ The Sanatorium staff. The authors are indebted to all the physicians at the Georgia State Sanatorium and to Dr. Max Pinner for kind criticism and advice during the preparation of this paper.

sees and treats a good percentage of our discharged patients. He (2) has said, "It is urged that pneumoperitoneum be recognized as a collapse measure of considerable value and promise and that it be given a trial in properly selected cases."

PHYSIOLOGY

Pneumoperitoneum differs from artificial pneumothorax in that artificial pneumothorax tends to neutralize the subatmospheric intrapleural pressure, thus allowing the lung to collapse, while pneumoperitoneum lessens the intrathoracic volume by elevation of the diaphragm, thus reducing the available intrathoracic space. As a result of this lessening of lung volume the more diseased areas in the lungs tend to collapse and heal more rapidly, just as in pneumothorax. It is seen that the approach to these two different forms of therapy is dissimilar. The result, however, appears to be the same.

Several physicians have thought, and the impression seems to be fairly general, that this form of basal collapse provided by a phrenic nerve crush and pneumoperitoneum is particularly beneficial in the treatment of basal lung disease. Some of us at this institution have not felt that this is true. We have regarded the intrapleural space as a closed cavity, responding to outside influences according to known laws of physics. Any pressure change from without will be equally distributed to all parts of the intrapleural and thoracic cavities. For this reason an apical cavity or apical disease should respond in the same manner to basal collapse as basal disease.

The major change taking place after the induction of pneumoperitoneum is, as said before, the reduction in total lung volume. In 4 cases of *established* pneumoperitoneum in which artificial pneumothorax was induced, the intrapleural pressure was found to be well on the negative side, approximating that found in the normal intrapleural space rather than the somewhat higher, yet still negative intrapleural pressures usually found in uncomplicated cases of established pneumothorax. There is probably present an initial rise in intrapleural pressure following induction of and refills of artificial pneumoperitoneum. It seems reasonable to assume, however, that the mechanics and physiology of the intrapleural space are less altered by an established pneumoperitoneum than by an established pneumothorax.

In individual cases there may be interfering factors which may prevent complete and even transference of pressure changes from the peritoneal cavity to the thoracic cavity. These factors include previous pleurisy with obliteration of the intrapleural space, adhesions of the diaphragm and pleura to the thoracic wall and mediastinal structures, and adhesions of the peritoneum to the diaphragm and abdominal contents. In the large majority of our cases, results indicate that there is no significant difference in the healing response of any section of the lung, following therapy with pneumoperitoneum and phrenic nerve crush. Since both physiological reason and actual results show this to be true, we feel that the time has come to disregard the previous opinion that this type of collapse was indicated only in basal disease.

It is well known that long-standing tuberculous disease responds to collapse therapy less readily than early disease. It is also well known that tuberculosis usually appears first in the apical portions of the human lung, and consequently is more likely to be fibrotic than fresher areas lower in the lungs. For this reason alone it is seen that thick-walled cavities in the apices of lungs will not respond so readily to *any* type of therapy as will fresher disease, wherever it is located in the lung.

METHOD

Our method of inducing pneumoperitoneum following a phrenic nerve crush for treatment of tuberculosis is well covered in the report by Crow (1). Briefly, the patient lies supine on the table and the abdomen is prepared in a way similar to that in which the chest is prepared for giving pneumothorax. The patient is advised not to eat a hearty meal prior to the induction of therapy. A small wheal is produced with 1 per cent procaine hydrochloride in the area of the left upper abdominal quadrant. Procaine hydrochloride is then introduced into the deeper tissues down to the peritoneal cavity. Then air is introduced by means of a regular pneumothorax apparatus. The type of needle used is unimportant, depending upon the individual skill or preference of the operator. We have found all pneumothorax needles satisfactory. Approximately 500 to 700 cc. of air are introduced into the peritoneal cavity on first injection. The patients complain usually of slight pain in the shoulders and in the epigastrium due either to peritoneal irritation caused by the air, or to stretching of previously present diaphragmatic adhesions. This pain wears off in several days and the patient has no symptoms whatever in an uncomplicated case. These two symptoms are an actual sign that the air has been introduced into the right space. On the second day 500 to 700 cc. of air are again introduced. A day is then skipped and then 500 to 700 cc. of air are again introduced. From then on the patient can go on a semi-weekly, weekly, or ten-day schedule, depending upon the individual requirement of the patient. We have found that an average of 1,000 cc. of air introduced every seven days seems to be about an optimum. Rilance and Warring (3) report using from 500 to 700 cc. weekly, whereas we feel that 1,000 cc. of air per week more nearly approach the patient's tolerance and at the same time yields a maximum response to therapy.

REPORT OF CASES

The following are the results in a series of 110 colored patients treated for tuberculosis during the past six years at this institution by phrenic nerve crush and artificial pneumoperitoneum.⁴ It is the first recorded appreciable series of Negroes receiving this form of therapy.

These 110 patients stayed in the hospital an average of 14.6 months. The average duration of this therapy is fifteen months. Twenty per cent of the patients in the series have received their pneumoperitoneum for periods ranging

⁴ This form of therapy was initiated and given for the most part during this period by Drs. J. E. McLain, J. B. Ford, Jr. and one of us (N.L.A.).

from only three to twelve months. The majority of them have improved so strikingly, even with such a short duration of therapy, that they are included in the series. As a result, the average duration of therapy, fifteen months, is considerably shorter for the entire series than it is for 80 per cent of the patients who had received air anywhere from twelve months to four years.

The follow-up investigation of scattered Negro patients in Georgia is difficult. In an effort to investigate the result of each discharged case, only one patient was not contacted, and this case was not included in the series. Because the senior author was leaving the state, follow-up observations could not be continued for a longer period of time. It is doubtful, however, if accurate statistical results could be obtained easily for longer periods of time in any appreciable series of cases.

The ages of these patients ranged from 15 to 55, with an average of 29 years. Of these cases 61, or 55 per cent, were females and 49, or 45 per cent, were males.

During therapy these 110 patients had an average weight gain of $7\frac{1}{2}$ pounds each; 69 gained an average of 15 pounds, 6 had no appreciable change and 35 lost an average of 7 pounds.

Of the 110 patients, 99 were febrile and 11 were afebrile prior to therapy. At the present time 23 are febrile and 76 are afebrile, thus representing a "conversion" of 76 per cent.

Ninety-one patients had positive sputa on admission; 19 were negative. Now 40 have positive sputa and 70 have negative sputa. This is a conversion of sputum of 56 per cent. All sputa were examined by direct smears, concentrated and cultured if necessary. Gastric lavages were done if sputa were still negative on admission. Gastric lavage specimens were examined by direct smear, concentrated and cultured if necessary, and inoculated intraperitoneally into guinea pigs. Gastric lavages were not done on discharged cases with negative sputa due to shortage of personnel and guinea pigs. Thus the sputum conversion percentage is somewhat higher than it would actually be if gastric lavages could have been done on all discharges.

Ninety-five patients, or 85 per cent, had exudative disease, 11 mixed, 2 pneumonic, one frankly productive and one miliary. The tuberculous disease seen here in Negroes is predominantly exudative. Our figures, of course, show this predominance, and thus no significant figures regarding the use of pneumoperitoneum and phrenic nerve crush in productive disease can be given from this series.

Sixty-nine (63 per cent) had no previous therapy. Thirty (28 per cent) had previous artificial pneumothorax, 2 had previous bilateral artificial pneumothorax and 4 had previous thoracoplasties. One had a previous phrenic nerve crush which had been done several years previously. Four patients had previous pneumonolyses.

Fifty-six had right phrenic nerve crushes at the onset of the therapy; 48 had a left phrenic crush at the onset of therapy. Five patients had no phrenic nerve crush prior to the induction of pneumoperitoneum. In these 5 patients it was

not thought that a phrenic nerve crush was indicated. Nine cases (8.2 per cent) were conditioned for thoracoplasty by this method of therapy. Only 2 of them, however, were found to need the operation following pneumoperitoneum. These 2 cases received thoracoplasties and have now arrested disease.

Cases which received therapy for less than three months are not included, since it was felt that a fair trial of phrenic nerve crush and pneumoperitoneum should continue for at least three months. There were 11 patients who did not receive this form of therapy for as long as three months. Six of these failed to return from leave of absence and 5 of them left the Sanatorium against medical advice. Some of these continued pneumoperitoneum at home and improved, but they are not included, since we did not feel that their group had given the therapy a fair trial. Two other cases died after they had been discharged, after pneumoperitoneum was stopped against advice. One patient had a recurrence of pulmonary disease following discontinuance of pneumoperitoneum.

Four other patients had to wear trusses to prevent the air in the peritoneal space from causing severe hernias. Three of these trusses were of the inguinal type and one was umbilical. All trusses prevented leakage of air and pneumoperitoneum was continued satisfactorily. In certain cases, wide adhesive tape plasters over the umbilicus prevented any ballooning of potential umbilical hernias due to pneumoperitoneum. One case died of heart failure after the pulmonary disease was apparently arrested by the pneumoperitoneum and phrenic nerve crush. This heart disease was present prior to therapy. Ten other patients had heart disease (9 hypertension), and all but one of these had no trouble with this form of therapy.

Pneumoperitoneum was started in one patient to stop hemoptysis. This patient eventually died, although his hemoptysis was apparently stopped by this form of treatment. In one patient pneumoperitoneum was discontinued because of dyspnea.

Table 1 shows that 73 (66 per cent) of these patients were far advanced at the onset of therapy, 36 (33 per cent) moderately advanced and one (1 per cent) minimal. There is no significant variation in the sexes here.

It is seen that 13 per cent of the patients had a hopeless prognosis on admission. Fifty-four per cent had a very poor prognosis. In 18 per cent the prognosis was questionable. Only 15 per cent had a good prognosis at the onset of therapy. This indicates that the results might be even more favorable if the cases are properly selected. There is no significant difference in prognosis between the sexes.

It is seen that 11 per cent of the cases were arrested, 22 per cent apparently arrested, 27 per cent quiescent and 23 per cent improved. Only 17 per cent of these patients, unselected as they were, were not improved by this form of therapy. Twenty-three per cent of these cases have discontinued therapy and have shown no recurrence of disease during two or more years. Four patients, or 25 per cent of the unimproved cases, had a recurrence of disease following cessation of therapy. There is no significant variation in the response of the opposite sexes to this form of therapy as shown by this table.

It is seen in table 2 that, out of 113 cavities originally seen, 66 (58.4 per cent) were closed, 12 (10.6 per cent) were smaller than at the onset of therapy and 35 (30.9 per cent) were larger or unchanged following therapy. Diagnosis of cavity closure was based on serial X-ray examinations before, during and following therapy. In each case X-ray evidence of cavity closure was confirmed by negative sputum examinations. Two so-called tension cavities with persistent

TABLE 1

Classification of all patients according to diagnostic classification, prognosis, results and sex

	TOTAL	FEMALES	MALES
<i>Diagnosis</i>			
Far advanced (d).....	4 (3%)	2 (2%)	2 (2%)
Far advanced (c).....	36 (33%)	22 (20%)	14 (13%)
Far advanced (b).....	33 (30%)	19 (17%)	14 (13%)
Moderately advanced (c).....	3 (3%)	0	3 (3%)
Moderately advanced (b).....	30 (27%)	16 (14%)	14 (13%)
Moderately advanced (a).....	3 (3%)	1 (1%)	2 (2%)
Minimal (b).....	1 (1%)	1 (1%)	0
	110 (100%)	61 (55%)	49 (45%)
<i>Prognosis</i>			
Hopeless.....	14 (13%)	8 (7%)	6 (5%)
Very poor.....	60 (54%)	33 (30%)	27 (26%)
Questionable.....	20 (18%)	12 (11%)	8 (7%)
Fair.....	15 (14%)	8 (7%)	7 (6%)
Good.....	1 (1%)	0	1 (1%)
	110 (100%)	61 (55%)	49 (45%)
<i>Results of Therapy</i>			
Arrested.....	12 (11%)	8 (7%)	4 (4%)
Apparently arrested.....	24 (22%)	14 (13%)	10 (9%)
Quiescent.....	30 (27%)	19 (17%)	11 (10%)
Improved.....	25 (23%)	9 (8%)	16 (15%)
Unimproved (frankly active).....	9 (8%)	4 (4%)	5 (4%)
Died.....	10 (9%)	7 (6%)	3 (3%)
	110 (100%)	61 (55%)	49 (45%)

spherical configuration failed to be altered by this therapy. The response of cavities at different sections of the lung are remarkably similar. It is seen that 58.6 per cent of apical cavities were closed, 57.7 per cent of mid-zone cavities and 58.8 per cent of basal cavities. These figures are significant since they reveal that cavities in any section of the lung may respond equally well to phrenic nerve crush and pneumoperitoneum.

Table 3 indicates clearly that far advanced disease responds less favorably to therapy than moderately advanced or minimal disease. The results in

moderately advanced tuberculosis are so good that it is hoped that this form of therapy will be tried much more extensively for disease of this nature. So far we have not had enough cases of minimal disease to draw any conclusions.

TABLE 2
Classification of cavities and their response to therapy

	ENTIRE LUNG	APICAL	MIDZONE	BASAL
Closed.....	66 (58.4%)	41 (58.6%)	15 (57.7%)	10 (58.8%)
Not closed				
(a) Smaller.....	12 (10.6%)	6 (8.6%)	4 (15.4%)	2 (11.7%)
(b) Larger or unchanged...	35 (30.9%)	23 (32.8%)	7 (26.8%)	5 (29.4%)
Totals.....	113 (100%)	70 (62%)*	26 (23%)*	17 (15%)*

* Percentage of total cavities.

TABLE 3
Results of therapy classified by diagnosis and sex

	TOTAL	WOMEN	MEN
<i>Far advanced</i>			
Arrested.....	6 (9%)	5 (12%)	1 (4%)
Apparently arrested.....	12 (17%)	6 (14%)	6 (21%)
Quiescent.....	20 (28%)	16 (37%)	4 (14%)
Improved.....	14 (20%)	5 (12%)	9 (32%)
Unimproved.....	9 (12%)	4 (9%)	5 (18%)
Died.....	10 (14%)	7 (16%)	3 (11%)
	(100%)	(100%)	(100%)
<i>Moderately advanced</i>			
Arrested.....	6 (16%)	3 (18%)	3 (14%)
Apparently arrested.....	11 (29%)	7 (41%)	4 (19%)
Quiescent.....	10 (26%)	3 (18%)	7 (33%)
Improved.....	11 (29%)	4 (23%)	7 (33%)
	(100%)	(100%)	(100%)
<i>Minimal</i>			
Apparently arrested.....	1	1	0
Totals.....	110	61	49

There seems to be no significant variation in the response of the opposite sexes to therapy, regardless of how advanced they are at the onset of treatment.

COMPLICATIONS OF THERAPY

These complications are presented not to discourage this form of treatment, but to outline most of the possible dangers and complications and to show how they may be overcome or avoided.

Perhaps the most severe possible complication is air embolism. We have not experienced this complication in any of our cases.

Perhaps the second most severe complication is tuberculous peritonitis. This may be preëxisting, and probably is in the majority of cases. This complication has appeared in approximately 1 per cent of cases. Some of the patients with this complication may be salvaged by removing all the air from the peritoneal cavity along with any peritoneal fluid which may have accumulated.

Peritoneal adhesions were seen on abdominal X-ray films in 71 per cent of our cases. In the majority of these cases they did not cause any trouble. However, in some cases they will prevent a satisfactory rise of the diaphragm.

In approximately 8 per cent of the patients a peritoneal effusion is seen to be present in the dependent areas of the peritoneal cavity. This fluid serves as a warning not to increase intraperitoneal pressures to too high a level. In the great majority of these cases this peritoneal effusion is sterile and will not cause any complication.

Dyspnea is present in approximately 6 per cent of these patients. This may be gradually overcome by increasing the doses of air very slowly until the patient becomes adjusted to this therapy.

In certain cases pressures above 10 cm. of water are encountered. Although this complication serves as a warning, it does not necessarily preclude the continuance of pneumoperitoneum. Satisfactory intraperitoneal pressures following refills average around 5 cm. of water in well established cases.

We have observed a tendency toward an obliterative peritonitis in one patient. This caused an increase of intraperitoneal pressure but has not necessitated discontinuance of therapy.

Pregnancy, of course, provides a complication of pneumoperitoneum. Each case is dealt with individually, the pneumoperitoneum usually being discontinued regardless of what disposition is made of the fetus.

Severe heart disease following the induction of pneumoperitoneum has been seen in only one of our cases. In this patient treatment was discontinued and the patient showed no ill effect. It is granted that severe heart disease is a contraindication to this form of therapy, and this is borne out by the fact that one of our cases died of heart disease preëxistent to therapy. In about 10 per cent of our cases there is some preëxisting cardio-circulatory disease. If this is not too severe and the patient is watched closely, it will not contraindicate therapy. Recently one of us (N. L. A.) observed the appearance of a pericardial friction rub in a patient receiving pneumoperitoneum. This disappeared when refills were temporarily stopped.

In a very few patients spontaneous rupture of the diaphragm may occur when there is far advanced disease and an erosive, ulcerative tuberculous process of the diaphragm. In this complication a spontaneous pneumothorax will usually occur, the air passing from the peritoneal cavity into the intrapleural space. Removal of air from both below and above the diaphragm will relieve dyspnea; pneumoperitoneum should be abandoned.

Another possible complication is passage of air through the aortic or the esophageal hiatus up through the mediastinum into the tissue spaces and fascial

planes of the neck. This has occurred in one patient. No damage was sustained and the only difficulty was a temporary cessation in the giving of large doses of air.

Occasionally the operator will introduce air into the tissue spaces in the abdomen. This is more uncomfortable to the patient than it is serious.

After the induction of pneumoperitoneum, approximately 4 per cent of all patients will complain of some pain requiring sedation. This pain, however, disappears rapidly within two days to a week as the patient becomes accustomed to his pneumoperitoneum.

Patients with a tendency toward herniation anywhere in the abdomen are, of course, potential risks. The use of umbilical and inguinal trusses, however, has obviated any difficulty we have experienced in giving pneumoperitoneum to patients with either hernial weaknesses or actual hernia.

One patient developed pleurisy during the course of therapy. It is impossible to state whether or not this resulted from the therapy.

One patient had an acute appendicitis. Appendectomy was done without difficulty following removal of all the air in the peritoneal space. The patient has now arrested disease. Rilance and Warring (4) report an incidence of 7 per cent of acute appendicitis in patients receiving pneumoperitoneum.

Three patients had hemoptysis during therapy. This is an incidence of 2 per cent, and it is not felt that it occurred as a direct result of therapy.

Penetration of intestine, liver, spleen or kidney with the needle has not occurred to our knowledge. It is unlikely that this complication will occur if ordinary care is practiced.

ADVANTAGES OF ARTIFICIAL PNEUMOPERITONEUM OVER OTHER TYPES OF THERAPY

Artificial pneumoperitoneum has been regarded by Rudman (5) as a far more formidable procedure than artificial pneumothorax. At this Sanatorium we take issue with this statement; we feel that artificial pneumoperitoneum is a much safer procedure than artificial pneumothorax. The ordinary complications of artificial pneumoperitoneum are much less severe than those seen in the treatment of tuberculosis by artificial pneumothorax. We feel that the use of pneumoperitoneum has the following advantages over the use of artificial pneumothorax:

(1) Both lung fields can be observed by fluoroscopy or roentgenography, and shadows can be observed in their response to therapy. This cannot be done in a large percentage of pneumothorax cases, since the diseased portion is either hidden by the mediastinum or so much collapsed that it cannot be followed roentgenologically without reëxpansion. We emphasize that lung volume may be reduced as much as 70 per cent by this method of therapy, just as in artificial pneumothorax. At the same time most of the diseased areas which are collapsed may readily be seen during therapy with pneumoperitoneum.

(2) Pneumoperitoneum may be discontinued or continued again far more readily than artificial pneumothorax. Very little change is seen in the peri-

toneum in uncomplicated cases according to Trimble, Eaton and Moore (6). In contradistinction to the use of artificial pneumothorax, the complications of lost space, contralateral spread and spontaneous pneumothorax are not common.

(3) With the use of pneumoperitoneum, thickened pleura and nonexpandable lungs requiring oleothoraces, thoracoplasties and unroofing operations are seldom seen.

(4) The complication of tuberculous empyema is avoided by the use of pneumoperitoneum. This appears to be one of the most severe complications of pneumothorax, and, as any experienced tuberculosis specialist knows, the treatment of tuberculous empyema is far from satisfactory.

(5) Pneumoperitoneum treats bilateral disease at the same time with one procedure, whereas artificial pneumothorax usually must be carried on as a bilateral procedure in order to treat bilateral disease effectively. This, of course, provides a great saving of time to both patient and the doctor.

DISCUSSION

The records at this Sanatorium indicate that the results of artificial pneumothorax in the Negro are disappointing. It is believed that the lower economic status of the Negro and his innate desire to enjoy life strenuously at home contribute toward the development of pleural effusions, contralateral spreads and empyemata, all of which seem frequent in ambulatory pneumothorax cases. These complications so far seem much less frequent in the discharged ambulatory pneumoperitoneum cases.

It would seem premature at this time to list the indications for therapy with phrenic nerve crush and pneumoperitoneum. The therapy appears most logical in the treatment of bilateral disease although unilateral disease responds equally well if not better. Early disease confined to small areas responds most readily to any type of therapy.

Duration of therapy seems to parallel other forms of collapse therapy. Each case of course represents an individual problem. Since the handicap of pneumoperitoneum is much less than it might at first appear to be, many cases conduct normal lives during therapy. Patients with lax abdominal walls are encouraged to wear abdominal supporters to enhance therapy and reduce cosmetic inelegance.

If it can be shown that pneumoperitoneum supplementing a phrenic nerve crush will give results as satisfactory as, or approximating those of any other form of collapse therapy, then its obvious advantages over artificial pneumothorax, as previously stated, should really make it a treatment of choice in the majority of tuberculous patients. Any form of therapy must, of course, withstand the criterion of time, and it is hoped that more reports, covering longer periods of this therapy, will appear. It is our desire to emphasize the value of pneumoperitoneum and phrenic nerve crush so that it will be used more extensively throughout the country. We feel that we have tried it extensively in an appreciable series of both white and colored cases, and we believe that if it is fully applied to suitable cases the results will be as good or better than those seen with artificial pneumothorax.

SUMMARY AND CONCLUSIONS

1. A series of 110 colored patients receiving artificial pneumoperitoneum as a treatment of pulmonary tuberculosis is presented. Of these, 105 received a phrenic nerve crush prior to induction of artificial pneumoperitoneum.

2. This is the first recorded appreciable series of Negro patients receiving this form of therapy.

3. A discussion of pneumoperitoneum, its physiology, its method of use, its complications and its advantages is presented.

4. The importance of maximum elevation of the diaphragm is emphasized.

5. Of these 110 cases, 11 per cent are arrested, 22 per cent are apparently arrested, 27 per cent are quiescent and 23 per cent are improved. Eight per cent are unimproved and 9 per cent are dead. The patients were not carefully selected as suitable cases for this therapy and 14 per cent were regarded as hopeless at the onset of therapy.

6. Cavity closure occurred in 58.4 per cent. Of the apical cavities, 58.6 per cent were closed, of the mid-zone cavities, 57.7 per cent were closed and of the basal cavities, 58.8 per cent were closed.

7. Sputum conversion was observed in 56 per cent.

8. It is strongly felt that this form of therapy should be utilized in the treatment of tuberculosis throughout the lung, rather than largely confined to patients with basal disease. The reasons for this impression are given. The results bear this out accurately.

9. There appears to be no significant variation in the response of sexes to this form of therapy.

10. It is apparent from this series that early disease responds more favorably than far advanced disease.

11. It is hoped that pneumoperitoneum combined with phrenic nerve crush will be used much more extensively in the treatment of minimal and moderately advanced disease.

12. Artificial pneumoperitoneum combined with phrenic nerve crush should be used at all sanatoria maintaining a program of collapse therapy. We feel that it is equally, if not more, effective than artificial pneumothorax in the treatment of pulmonary tuberculosis, and at the same time avoids most of the complications of artificial pneumothorax.

SUMARIO Y CONCLUSIONES

1. En una serie de 110 negros con tuberculosis pulmonar se aplicó el neumoperitoneo terapéutico, y en 105 de ellos se aplastó el frénico previamente.

2. Esta es la primera serie apreciable de negros en que se haya comunicado el resultado obtenido con esta terapéutica observándose el resultado.

3. Preséntase aquí una reseña del neumoperitoneo, su fisiología, técnica, complicaciones y ventajas.

4. Recálcase la importancia de obtener una elevación máxima del diafragma.

5. De esos 110 casos, 11% están estacionados, 22% aparentemente estacionados, 27% quiescentes y 23% mejorados, mientras que 8% no han mejorado y

9% han muerto. Los enfermos no fueron seleccionados cuidadosamente como apropiados para dicha terapéutica y 14% estaban desahuciados al iniciarse la terapéutica.

6. En 58.4% se obtuvo cierre de las cavernas: cerrándose 58.6% de las apicales, 57.7% de las de la zona media y 58.8% de las basales.

7. En 56% se observó conversión del esputo.

8. Abrígate la convicción de que debe utilizarse esta terapéutica en la tuberculosis de cualquier parte del pulmón, más bien que limitarla en gran parte a los casos de afección basal. Preséntanse las razones en que se funda esta impresión cuya exactitud confirman los resultados.

9. No parece que exista variación significativa entre los dos sexos en la respuesta a esta terapéutica.

10. A juzgar por esta serie es evidente que la enfermedad temprana responde más favorablemente que la muy avanzada.

11. Espérase que el neumoperitoneo combinado con el aplastamiento del frénico sea mucho más usado en el tratamiento de los casos mínimos y moderadamente avanzados.

12. En todos los sanatorios que aplican la colapsoterapia deben utilizar el neumoperitoneo terapéutico combinado con el aplastamiento del frénico, pues parece mostrar tanto o más eficacia que el neumotórax terapéutico en la tuberculosis pulmonar, evitando al mismo tiempo la mayor parte de las complicaciones asociadas con el último.

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TUBERCULOSIS IN CHILDREN¹

A Comparison between Postmortem Material from Buffalo, New York and
Santiago, Chile

J. SCHWARZ

The more recent literature presents relatively few anatomical observations on infantile tuberculosis. Because of this, we think it should be of interest to present a comparative study of the differences observed between the material dissected in Buffalo and in Santiago; while Terplan (1) had at his disposal all the newest technical facilities, we had only in a few cases X-ray photographs for clinical purpose; X-ray photographs of postmortem lungs were unobtainable, as photographic material is scarce.

Nearly all the material has been autopsied by the author himself, some cases were examined by Vergara. The postmortem work comes from a General Children's Hospital in Santiago,² equipped with about 400 beds and with Departments of Surgery, Internal Medicine, Tuberculosis, etc. In comparison with Terplan's statistics, we observed a much higher number of tuberculous infections, especially in children above 6 years of age (table 1).

The frequency of tuberculous infection in Chile is caused principally by poverty and low standard of living, specially in the industrial areas, by lack of hygiene, certain defects in sanitary legislation which fails to eliminate contact infection and which can receive no detailed analysis here. We should only like to present table 2 which shows that Chile really has the highest tuberculosis mortality.

Very eloquent also is the number of tuberculin reactors in Santiago. School children give the reactions shown in table 3.

According to very interesting calculations by Straub (3), the numbers of yearly new infections are as follows:

- 1 out of every 10 if at 8 years of age there are 50 per cent tuberculin reactors
- 1 out of every 15 if at 11 years of age there are 50 per cent tuberculin reactors
- 1 out of every 20 if at 15 years of age there are 50 per cent tuberculin reactors
- 1 out of every 25 if at 18 years of age there are 50 per cent tuberculin reactors

In other words, in Santiago, Chile, the probability of a new yearly infection per person is approximately 1 in 8 (in U. S. A. 1 in 20 or 30, differing in the various regions); this means that out of the 5,000,000 Chileans approximately 625,000 acquire a new infection every year (in the U. S. A. this number is 250,000 per 5,000,000 of population, considering an average tuberculinization of 50 per cent at 15 years of age). If the exact statistics are examined, one will arrive at a number still more unfavorable for Chile.

¹ From the Pathology Laboratories of the Valdivia Regional Hospital and "Manuel Arriaran" Children's Hospital of Santiago, Chile.

² Hospital "Manuel Arriaran."

TABLE 1

Comparison between postmortem material from Buffalo, New York and Santiago, Chile

	TERPLAN			SCHWARZ		
	Number of autopsies	Number with tuberculous lesions	Per cent positive	Number of autopsies	Number with tuberculous lesions	Per cent positive
5 weeks-12 months.....	345	10	3.4	112	6	5.4
13 months-2 years.....	97	10	9.7	54	15	27.7
2 years-6 years.....	144	15	10.4	45	17	37.7
6 years-10 years.....	40	7	17.5	22	12	54.5
10 years-14 years.....	40	8	27.5	14	7	50
14 years-18 years.....	32	7	21.8	—		
5 weeks-6 years.....	586	35	5.9	211	38	18
6 years-18 years.....	113	22	19.4	36	19	52.9

TABLE 2

Mortality rate from tuberculosis (all forms) per 100,000 of population in 1937

1. Union of South Africa.....	36.5
5. Holland.....	48.9
6. United States of America.....	53.6
7. Canada.....	60.1
8. England and Wales.....	69.5
9. Germany.....	70.5
19. France.....	118.1
24. Finland.....	189.9
26. Chile.....	241.0

TABLE 3

Tuberculin reactors in Santiago, Chile (1943) according to Viel, Ncira and Fernandez (2)

AGE	NUMBER EXAMINED	POSITIVES	PER CENT
7- 8 years.....	752	450	59.8
9-10 years.....	1,065	749	70.3
11-12 years.....	1,017	756	74.3
13-14 years.....	510	394	77.2
15-16 years.....	76	54	75.0

Total population of Chile calculated for 1937, on the basis of the 1930 census: 4,597,254

Total mortality..... 109,759 (under 10 years of age 53,048)

Tuberculosis mortality..... 12,155 (under 10 years of age 1,535)

While in New York, with a population of 7,347,000 in 1939, only 118 children under 10 years of age died of tuberculosis, in Chile during 1937 twice as many died in hospitals only (224) and, in all the country, thirteen times that number (1,535).

For a close comparison with Terplan's work, we should like to follow roughly

his outline of work. In Terplan's 57 tuberculous cases, in only 35 was tuberculosis the cause of death; in our material we have observed 45. In none of the

TABLE 4
Anatomical findings in the material from Buffalo, New York and Santiago, Chile

THE CASES IN WHICH TUBERCULOSIS					
Was the cause of death			Was an incidental finding		
	Terplan	Schwarz		Terplan	Schwarz
A	23	26	I	5	1
B	3	18	J	1	8
C	3	—	K	6	—
D	2	—	L	3	1
E	1	—	M	2	
F	1	—	N	3	2 (our P)
G	1	1	O	2	—
H	1	—			
Total.....	35	45		22	12

A—Primary caseated (or calcified complex in lung and broncho-mediastinal lymph nodes with hematogenous dissemination.

A₁—Primary caseated complex with hematogenous dissemination.

A₂—Ghon focus not found; broncho-mediastinal lymph nodes in different stages of infection and hematogenous dissemination.

A₃—Ghon focus calcified, broncho-mediastinal lymph nodes in different stages of infection and hematogenous dissemination.

A₄—Active Ghon focus and hematogenous dissemination complicated with epidemic meningitis, diphtheria, etc.

B—Primary caseated (or calcified) complex in lung; intrabronchial and hematogenous dissemination.

C—Primary caseated complex and almost exclusively intrabronchial spread.

D—Postprimary chronic pulmonary tuberculosis with hematogenous dissemination.

E—Acute congenital tuberculosis.

F—Primary acute intestinal tuberculosis.

G—Selective hematogenous dissemination especially to the leptomeninx in connection with typical lymphoglandular exacerbation.

H—True reinfection with caseated complex of reinfection and hematogenous tubercles.

I—Primary caseated complex in active stage with isolated hematogenous tubercles.

J—Primary fibrous cheesy complex (closed).

K—Primary calcified complex with single or double pulmonary Ghon focus.

L—Primary calcified pulmonary focus without lymph node change.

M—Primary multiple cheesy fibrous foci in different lobes without changes in broncho-mediastinal lymph nodes.

N—Calcified mesenteric lymph nodes.

O—Calcified complex with intrabronchial localization of primary focus and additional calcified lesions with collapse induration.

P—Intestinal tuberculosis with caseated mesenteric lymph nodes.

cases have we seen the intestine as the portal of entry for later generalization, and in only 2 cases have we observed intestinal foci (nos. 1 and 22), in both with no more complications than caseated mesenteric lymph nodes. This circum-

stance of few intestinal infections is very surprising considering the low standard of general hygiene. Apparently this is much influenced by the insignificant quantity of milk consumed in Chile.

Per capita milk consumption, per year, in liters

Switzerland.....	671	Netherlands	569
England.....	403	U. S. A.....	363
Germany.....	362	Argentina.....	101
Chile.....	50.5		

Surely these data need no comment.

In this country practically no pure, uncooked milk is consumed; it is nearly all used in the preparation of coffee, cakes, etc. and is therefore, sterilized when it reaches the consumer. Among his 57 cases, Terplan finds 4 primary intestinal infections (7 per cent); we have only 2 (3.5 per cent). It should be noted that in both cases subsequent cultivation and inoculation gave colonies of human tubercle bacilli.³ In the Netherlands the frequency of intestinal infection in recent years has been very high (Straub (3)), nearly 50 per cent of the total number of infections. In Germany statistics show a great difference, according to the regions—Beitzke (4), Berlin, 16 per cent; Wagener (5), Kiel, 21 per cent; Puhl (9), Freiburg, 1.8 per cent, etc. Ghon (6) reported 1 per cent of intestinal infections in Prague; Wallgren-Klercker (7) 2 per cent in Oslo and 25 per cent in rural districts.

Table 4 presents a brief comparison between Terplan's and our cases.

We see immediately the difference between Terplan's material and ours.

In the group of children whose cause of death was tuberculosis, there is a notable number of cases with combined hematogenous and bronchogenous dissemination (Terplan, 8.6 per cent; Schwarz, 40.0 per cent). In our material we note the absence of congenital tuberculosis cases and Terplan's C-F and H groups. And if Terplan comes to the conclusion that his 61.4 per cent mortality rate among all tuberculous cases is high, our number of 78.9 per cent is still higher and we still have to consider the existence of children who died in a meningococcic epidemic, so that probably in years of no epidemic our number would be still higher.

In all cases where the Ghon focus was found to be caseated—and this condition is found in the majority of children—a circumscribed, generally round or oval focus with sharp limits, frequently in subpleural localization, was encountered. If the primary focus has a subpleural location, the pleura nearly always shows a fibrous or nodular specific reaction. Such a circumscribed caseous and frequently subpleural round focus was accepted without doubt as primary or Ghon focus, if the regional lymph nodes were also found to be caseated. But such apparently clear cases must be, and were, cut into thin sheets in order to look for other, perhaps older or smaller, foci. Naturally, this was seldom found in children's lungs. The diagnosis of multiple primary foci is not difficult if the suspicious lesions are found in different sides of the lungs, or at least in

³ We thank Dr. Fl. Fuenzalida for his kind collaboration.

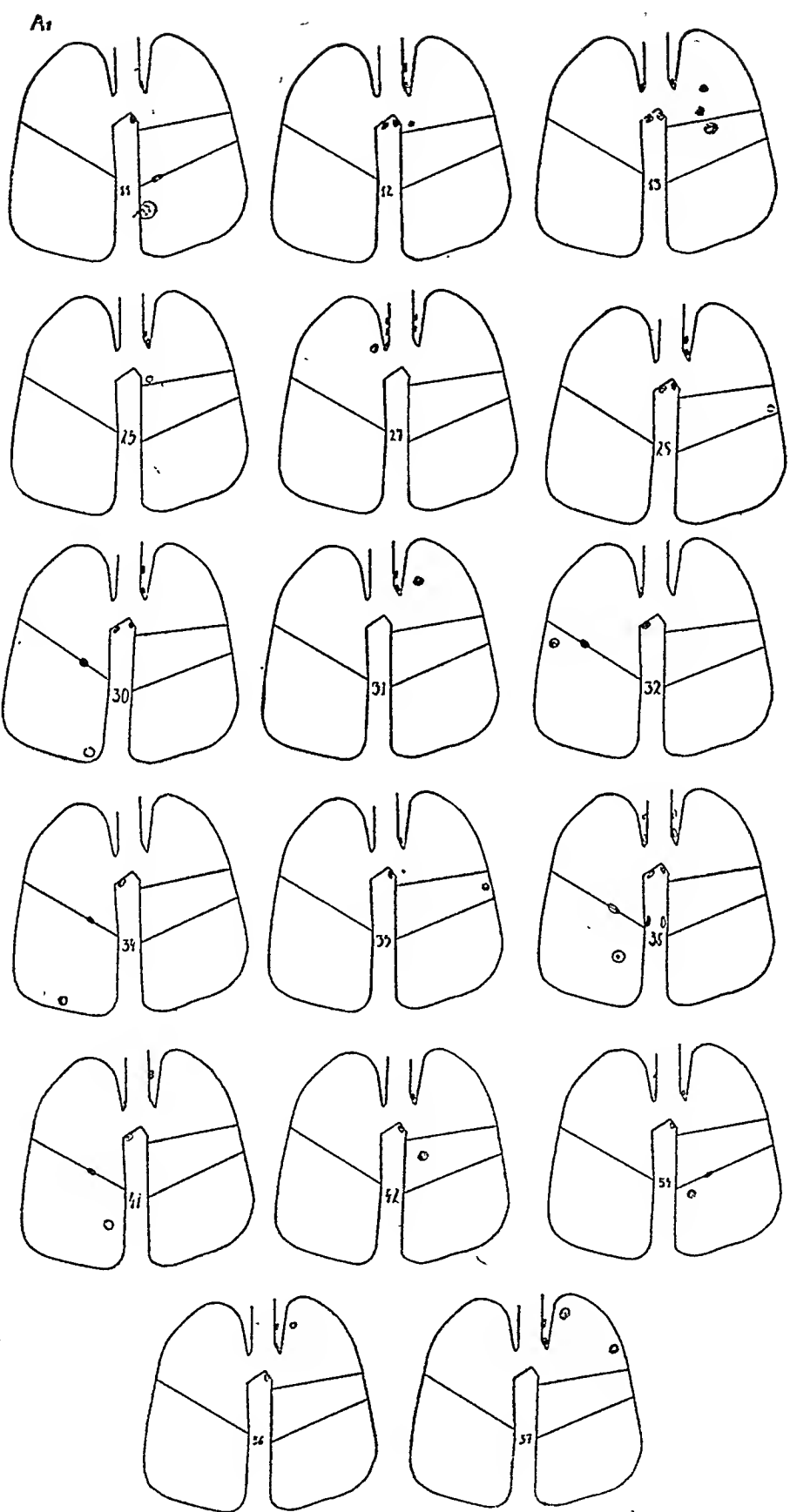
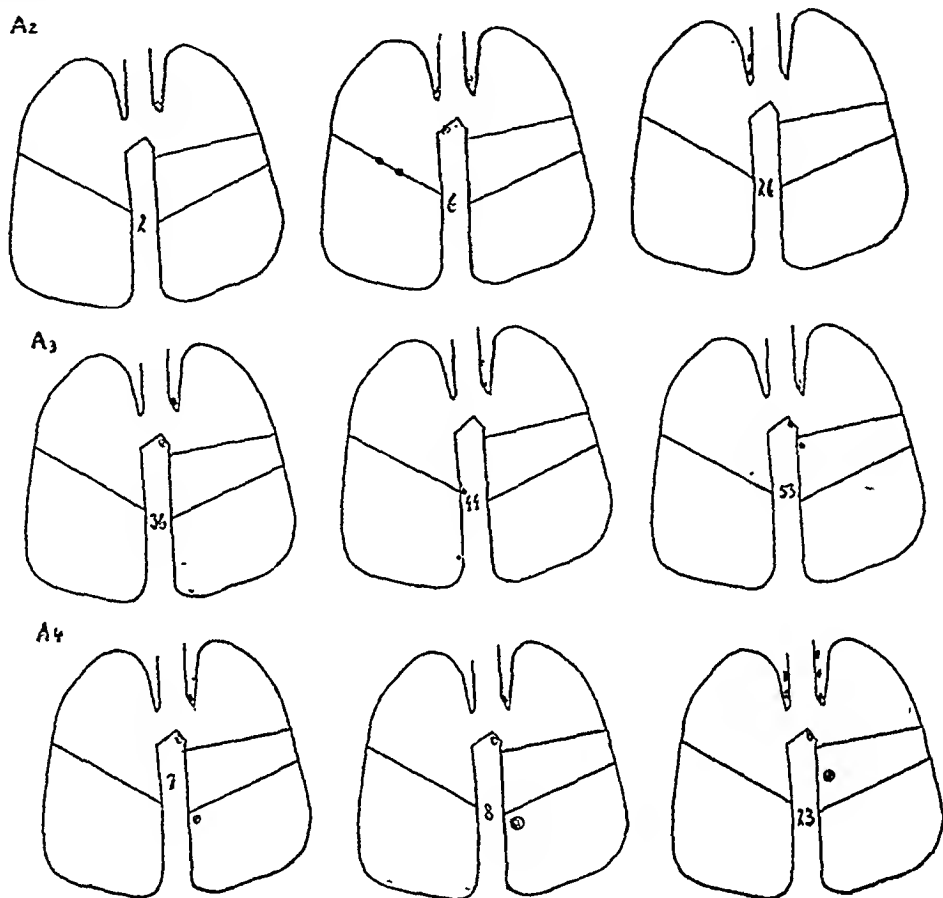


FIG. 1

different lobes, because then the lymph node component of the primary complex permits the establishment of the pathogenetic character of the focus.



KEY TO SCHEMES:	
○	LYMPH NODE
○	GHON FOCUS
⊕	ACINOUS TUBERCULOUS PNEUMONIA
☆	CAVITATION
•	CALCIFICATION
■	CASEOUS TUBERCULOSIS
	GELATINOUS PNEUMONIA
~	ATELECTASIS
∅	TUBERCULOUS HYPERPLASIA

FIG. 2

Our criteria for a diagnosis of the Ghon focus depends, in the first place, on the form, location and aspect of the focus, and on the presence of corresponding lymph node changes. If more than one suspicious focus is found in a pul-

B

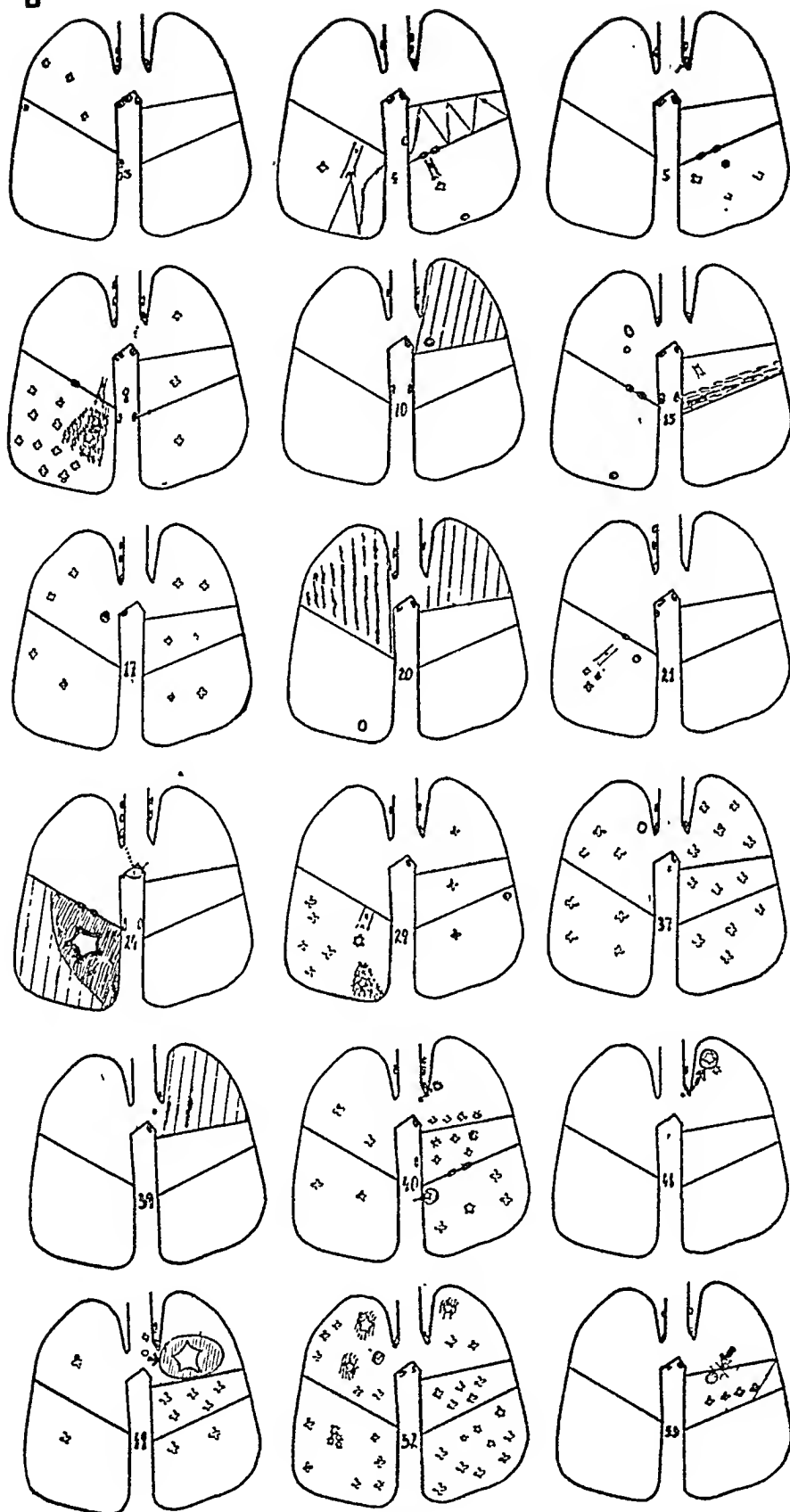


FIG. 3

monary lobe, the diagnostic help given by the lymph nodes disappears. In such cases, we have described the anatomical finding extensively in order that the reader may form his own opinion. With the exception of a few cases, such as cavernous phthisis where the finding of the Ghon focus was impossible, the calcified focus in children's lungs could be found easier than in adult's lungs due to the softness of children's organs.

We wish to add a few words about the diagnosis of the primary cavity. With the evolution of the cavity from the caseated to a liquefied focus, followed by the expulsion of the liquid masses, the focus itself naturally disappears but the caseated wall of the cavity remains together with the regional lymph nodes with their typical changes. It is certain that X-ray photographs are very helpful in discovering additional lesions, but we think that careful "classical" anatomical work, especially in children, can reduce failures to a minimum.

Figures 1, 2 and 3 present in schematic form the distribution of intrathoracic tuberculous lesions in our material (compare groups with table 4).

A. CASES WITH A CASEATED (OR CALCIFIED) PRIMARY PULMONARY COMPLEX WITH HEMATOGENOUS DISSEMINATION

The primary focus of the 26 cases of this group was found to be partially or completely caseated in 20 cases, with a total of twenty-three foci (there were in one case three and in another two Ghon foci). Sixteen Ghon foci were 6 mm. in diameter or smaller, ten were larger; the biggest focus had a diameter of 3 cm. (no. 8). Three Ghon foci were completely calcified, one only was the size of a grain of millet. In 2 cases the focus had a caseated centre but had a thick

TABLE 5
Distribution of Ghon foci in the pulmonary lobes

		LOBES				
		Right			Left	
		Upper	Middle	Lower	Upper	Lower
Schwarz {	Number.....	17	8	12	6	13
	Per cent	30.3	14.3	21.4	19.7	23.2
Hesse (8),	per cent.....	28.0	10.1	18.6	14.0	26.4
Puhl (9),	per cent.....	32.1	10.7	17.1	28.5	11.6
Lange (10),	per cent.....	24.1	6.5	22.9	25.3	21.2
Blumenberg (11),	per cent.....	33.5	11.6	18.1	22.3	14.5
Terplan (1),	per cent.....	25.0	20.8	4.1	16.6	32.2

fibrous capsule and in 2 other cases the Ghon focus had a calcified centre and a cheesy-fibrous periphery. In 3 cases the focus was not found, but its presence in the Lung may be taken for granted, as caseated or calcified broncho-medastinal lymph nodes were found. The foci were distributed in the pulmonary lobes as shown in table 5.

The total number of foci found in the 23 cases was twenty-six, because in case 13 we found three and in case 57 two. Three cases showed cavity formation within the primary focus (nos. 11, 13 and 8). In case 11 we saw a cavity of a

diameter of 2 cm. with a broad caseated margin; it had a rupture into the pleura, thus a pyopneumothorax was formed. In case 13 the biggest of the foci was about 30 x 11 x 18 mm. with a central cavity 13 mm. in diameter. A second Ghon focus in the right upper lobe had a central liquefaction, with perforation into the bronchus. In case 8 the cavity had a diameter of 3 cm., which is enormous for the lung of a 16 months old boy. In 3 further cases (nos. 23, 38 and 57) we found liquefaction of the centre (in case 57 in both primary foci). An intense perifocal spread was observed in only 3 cases (nos. 27, 31, 34) but we may affirm that generally we found pleural infection over the focus in almost every case, especially if the latter was immediately subpleural. Also, nearly always, even in cases without miliary spread in the lungs, millet-sized nodules were found around the focus and repeated microscopic study revealed a lymphogenous pathogenesis and the formation of visible tubercles exactly on the crossing of two or more lymphatic capillaries. These lymphogenous miliary tubercles were observed chiefly between the focus and the pleura.

Cases with more than one focus merit a special note.

Case 13: In the right middle lobe we found a focus, about 30 x 11 x 18 mm., with a large central cavity. Another caseated focus, with all the characteristics of a Ghon focus, was found near the base of the right upper lobe, subpleural near the anterior surface. It was about 12 x 6 x 6 mm. and had a central ulceration. A third pea-sized focus, completely caseated, was observed 1 cm. above the second one. While it seems to us that the first two foci may undoubtedly be declared to be primary, in this last case one would think it might be a secondary focus. In the first place, there would be no advantage in examining the lymph node, since both foci are situated in the same lobe; second, it is much smaller than the two first ones; and, last, there was a bronchial perforation in the second focus; therefore it would not be surprising if a caseated focus was found near this perforation. As for the circumstances that affirm the possible existence of three primary foci, we have the complete caseation of the third focus in a child of 18 months, where infection necessarily must have been massive (size of biggest focus, softening of both foci which point to the fact that this last focus was produced either at the same or almost the same time as the other two). The localization above the second focus in the bronchial perforation does not exclude a direct relation with this finding, but we would rather expect the production of secondary foci below the bronchial perforation and not above it. The shape and subpleural localization also lead us to suppose that this is really a case of three primary foci.

Case 57: In the right upper lobe we found a pea-sized, completely caseated focus with a central liquefaction. It was situated in the lower third of the lobe, near the anterior margin and subpleurally. The second caseated focus was observed in the same lobe, but 3 cm. below the apex. It was slightly larger than the first one. This focus was also completely caseated and had a central liquefaction and we had the impression of a parallel evolution of both foci so far as their age is concerned. Naturally in this case it is also impossible to determine, by means of studying the lymph nodes, whether they really are two primary foci, since they are both situated in the same lobe.

In 15 cases of the 26 of this group tuberculous meningitis was proved by autopsy, with several or numerous miliary tubercles in the leptomeninx. In

9 cases it was possible to laminate the brain (without previous fixation). In 5 cases we observed tuberculomata (in case 7 without meningitis): nos. 7, 25, 27 and 53 with one tuberculoma of the cerebellum, no. 35 with cortical tubercles of the right and left *gyrus centralis anterior*. Terplan (1) declares he did not observe cerebral tuberculomata if there was no intense miliary spread in other organs, but in this group we have cases 7 and 27, where we found few miliary tubercles in other organs and we also observed this in group B, case 24.

B. PRIMARY CASEATED (OR CALCIFIED) COMPLEX IN LUNG; INTRABRONCHIAL AND HEMATOGENOUS DISSEMINATION

While Terplan (1) observed only 3 cases in this group, we had 18. Also in quality our material differs considerably from his; the majority of our cases excepting case 39 in which no primary focus was found, case 9 in which the focus was already calcified, case 15 with three caseated foci and cases 4, 5, 11 and 37 with a simple caseated focus) showed central liquefaction either in the shape of a minor ulceration (cases 3, 17, 20, 29, 52 and 55) or as a great primary cavity (cases 10, 24, 40, 48 and 49). Undoubtedly the liquefaction of the primary focus is in direct relation with, and has great importance for, intrabronchial dissemination. This group seems to us very interesting because of its great number and uniformity. It demonstrates that—at least in our material—bronchogenous dissemination is of great importance in the evolution of primary infection. If Huebschmann (12) says that the size of the focus is directly proportional to the importance and gravity of the tuberculous process, we cannot accept this as a rule without exceptions, but it may be applied in bronchogenous dissemination because an increase in the size of the primary focus causes central liquefaction with consecutive disastrous consequences. Therefore, it would be prudent to change the thesis that says “in malignant cases, extraordinarily large foci are found” to one saying “a large focus usually presents central liquefaction, which includes the danger of bronchogenous dissemination.”

We have observed only 2 cases under 1 year and 4 of 1 to 2 years of age; the other 12 cases were in children from 3 to 14 years. It is notable that no less than 13 of the 19 cases are girls. We may point to the fact that, in our material, tuberculosis was more frequent and more malignant in girls than in boys, although naturally not in the amazing proportion shown in this group. We cannot discuss the causes of this fact, because they are not more than mere suspicions or suppositions. According to our material we can affirm that bronchogenous dissemination in primary infection is produced in the first place if the focus is ulcerated and transformed into a cavity. Naturally there are foci replaced by a cavity that do not produce bronchogenous dissemination; but in our material the majority of bronchogenous dissemination has relation to an ulcerated focus. The liquefaction or ulceration of a primary focus always constitutes a very serious complication and we can say that a large focus has a worse prognosis than a small one under the same circumstances, because in a large one there is always the danger of central liquefaction.

Bronchogenous dissemination is diagnosed in the presence of typical acinous

or confluent acino-nodous foci, or when a caseous pneumonia is found. Undoubtedly any bronchogenous dissemination is produced either directly by the intrabronchial introduction of softened and infected material or by tubercle bacilli originating from ulcerated foci of the bronchial or tracheal mucosa. In a study with Peña and Meneghello (13) we have described numerous cases where it was possible to determine exactly the point where the infectious masses entered the bronchus.

The great number of foci with central liquefaction in our material seems surprising to us. In group B there were no less than 11, that is, the majority of all foci observed. In group A, 6 cases had eight primary foci with central liquefaction, 2 of the cases having multiple Ghon foci (nos. 13 and 57).

This fact cannot be explained satisfactorily by the influence of race, sex or age, and we have to confess our lack of basic knowledge that would let us find its cause. We can point to the fact that in our Chilean material central liquefaction of the primary focus is frequent and is usually found together with bronchogenous dissemination. In group B all cases showed hematogenous dissemination in the lung, liver and spleen, while only 12 cases showed miliary tubercles in the kidney. We want to give special consideration to the presence of intestinal ulcers found in 13 out of 17 cases of group B (we did not have all the facts concerning the intestine of case 15), while in group A only 10 out of 26 cases had specific intestinal lesions (76.5 against 38 per cent). We are not surprised at the frequency of intestinal ulceration in cases of bronchial tuberculosis, but it shows the importance of bronchial infection for elimination of the infected material. We also think that this fact reveals, indirectly at least, the relative scarcity of hematogenous pathogenesis of intestinal ulcers, while we find it more frequently in cases with bronchogenous dissemination. In spite of bronchial infections and of the presence of cavities and softened foci and in spite of the child's lack of resistance to tuberculosis, specific laryngitis was infrequent in our material; we explain this by the swiftness of evolution in infantile tuberculosis. In the adult, tuberculosis often continues developing for years; the mucosa of the larynx is frequently affected and constitutes a serious and important complication (Cohen (14), Donelly (15) etc.).

Among the foci in group B, in 4 the largest diameter was 35 mm. or more, in 5 it was 12 mm., in 2, 30 mm. and in 8, 6 mm. In group A only 10 out of 26 foci were larger than 6 mm. (38.4 per cent) and in group B, 11 out of 19 (58 per cent). These large foci are the ones which present central liquefaction caused either by anatomical influences (lack of circulation) or by massive infection. We see in our material that liquefaction and the formation of a primary cavity depend chiefly on the size of the focus and, only because of this, should a large focus from the first moment onward have a worse prognosis than a small one.

A case of probable endogenous reinfection in this group deserves some special considerations (*case 9*). She was a 3 year old girl with a nearly completely calcified focus, subpleural near the base of the right inferior lobe. In the left inferior lobe we found a tuberculous endobronchitis of a major bronchus which led directly to an immense caseated focus of

triangular shape with various small central cavities. We gave special attention to the right inferior and superior tracheobronchial lymph nodes which were found extremely large and caseated and which compressed the principal right bronchus without producing any atelectasis. We consider the presence of such large caseated lymph nodes quite exceptional in a case with a calcified focus, taking into account the child's young age. Generally speaking, the nodal part of a primary complex depends on the age of the focus and one does not usually find a calcified focus as in this case, with large caseated nodal bundles; all this points towards the supposition of an endogenous and lymphoglandular exacerbation (reinfection of Ghon). We also consider in this case the absence of atelectasis extremely interesting, since it failed to develop in spite of the intense compression and even deformation of the principal right bronchus and in spite of the "help" given by a hydrothorax of 200 cc. in the right pleural cavity.

We have repeatedly seen that the mere compression of the principal bronchi is not sufficient to produce extensive atelectasis, because the wall of the large bronchi is apparently too rigid and resistant. This case can be variously interpreted and we consider only the calcified primary focus in the lower right lobe as a certain primary focus. The examination of lymph nodes raises doubts. The following groups of lymph nodes were found to be completely caseated: upper and lower right tracheobronchial (plum-size), bilateral paratracheal (bean-size) posterior mediastinal (plum-size), bilateral hilar (strawberry-size) and the mesenteric, joined in a fist-sized bundle weighing 95 g. (in relation with an ulcerative tuberculosis of the intestine).

This description seems to point toward a generalized caseous lymphadenitis, very frequent in the childhood type in relation to the primary focus. Less probable seems the possibility of an exogenous reinfection with the formation of a new focus. The triangular focus in the lower left lobe could be a new Ghon focus; this is improbable because of the lack of caseated interlobar and left tracheobronchial lymph nodes and also because of the child's age, because the loss of tuberculous allergy in a child of 3 years, with the certain presence of a calcified focus, would be most extraordinary.

It is possible that bronchial tuberculosis in this case is either the cause or the consequence of the caseous focus in the same lobe; there are positive and negative arguments for both possibilities.

Saldias (17) recently published a study on lymph node tuberculosis and agreed with Ghon (18), Puhl (9), Huebschmann (12), Sweany (19) etc. in explaining the existence of caseated lymph nodes in the presence of an old focus as an endogenous reinfection; we consider this the most probable development in this case.

Case 15 also was exceptional; a girl of 21 months. We found three pulmonary foci, the largest one was bean-sized, in the left upper lobe, the second focus, situated one cm. below the first one, was pea-sized and the third one, in the lower left lobe, one cm. over the base was also pea-sized. All three were completely caseated and circumscribed, apparently of the same age. The following lymph nodes were found completely caseated: left interlobar (up to 30 mm. in diameter), upper and lower bilateral tracheobronchial (up to 12 mm.), anterior mediastinal (up to 30 mm.) and posterior mediastinal (up to 6 mm.). In the lungs, liver, spleen and kidneys we found miliary tubercles and also a pea-sized tuberculoma in the left *gyrus centralis posterior*, situated in the cortex but not touching the leptomeninx. In the principal bronchus of the right middle lobe we found an extensive ulcero-caseous bronchitis and a complete caseation of the inferior third of the corresponding lobe. The location of the bronchitis, in a bronchus opposite the foci, is rather

strange and we could even suppose this to be the consequence and not the cause of the caseation found in the right middle lobe. This girl also contracted diphtheria with thick membranes in the larynx and trachea that doubtlessly accelerated her death.

In the 18 cases of bronchial dissemination we already have noted the following macroscopic bronchial lesions:

(1) *Bronchial perforation caused by caseated lymph nodes* (cases 5, 24 and 55).

Case 5: Twelve year old boy with a caseated Ghon focus, bean-sized and subpleural in the posterior part of the upper third of the right lower lobe. Between many caseated lymph nodes was a walnut-sized one in the right lung-hilus. This lymph node produced a perforation of the anterior wall of the right principal bronchus. Acinous foci were in the right lower lobe.

Case 24: A 14 months old girl. Immediately below the bifurcation of the trachea we found a perforation of 2 mm., situated in the inferior wall of the main right bronchus; it led to a cavity corresponding to the lower right tracheobronchial lymph nodes which were entirely softened and ulcerated, forming a cavity whose limits were the main bronchi and the esophagus, respectively. This cavity had ample communication with another cavity corresponding to the upper left tracheobronchial lymph nodes; these, in turn, were in communication with a large cavity situated in the left lower lobe. We found a cavernous focus in the upper third of this lobe, traversed by many bronchi and blood vessels. The cavity was not yet rounded and its upper margin was formed by a triangular caseated zone which, in its turn, presented central liquefaction. This cavity had ample communication with the cavity situated in the upper left tracheobronchial region. The lower two-thirds of this lobe were occupied by caseous pneumonic foci. In the other pulmonary lobes we found miliary tubercles, also somewhat larger ones. In the spleen, liver and kidneys we discovered miliary tubercles and also larger ones, and in the brain a tuberculoma without meningitis and in the intestine many specific ulcers. Summarily, this is a case of a large focus in the upper third of the left lower lobe with completely liquefied regional lymph nodes in the lower tracheobronchial region, expanding toward the right main bronchus. There is communication between this cavity and another upper tracheobronchial one which, in its turn, stands in direct communication with the primary cavity. Formation of a caseous pneumonia in the lower two-thirds of the left lower lobe, apparently more closely related to the primary cavity than to the lymph node perforation on right side. We observed no bronchogenous foci in the right lung, apparently because the communication between the softened lymph nodes was wider and easier to pass through for the infected masses than the narrow perforation leading toward the right main bronchus.

Case 55: Perforation of the right mid-lobe bronchus by ulcerated and caseated interlobar lymph nodes with a nearly complete atelectasis of the right middle lobe. The strawberry-sized primary focus of this 4 year old girl was found in the same lobe and showed central liquefaction.

(2) *Bronchial perforations in relation with cavities* (cases 40, 48 and 49).

Case 40: Complete destruction of the right upper bronchus in relation with a giant primary cavity in the upper third of the same lobe and intense bronchogenous dissemination in all pulmonary lobes.

Case 48: Perforation of the right main bronchus at the entrance to a walnut-sized primary cavity situated in the upper part of the right upper lobe. Consequently we found a very dense bronchogenous dissemination in the three right pulmonary lobes.

Case 49: Perforation of the right upper bronchus at the entrance to a large primary cavity that occupies the upper two-thirds of the corresponding lobe. As a remarkable localization we may add, in this case, the presence of a lentil-shaped ulcer on the mucosa of the hard palate, with clearly visible tubercles in its red margins.

(3) *Bronchial ulcerations with or without perforation* (cases 9, 29, 39, 40, 4, 15 and 21).

Case 4: Ulcerative tuberculosis of the right middle and left lower bronchus with bronchogenous dissemination and atelectasis of the two lobes. The active Ghon focus we found in the right lower lobe and without relation to the ulcerative bronchitis.

Case 9: See page 402.

Case 15: Ulcerative bronchitis of the right mid-lobe bronchus and complete caseation of the lower third of the corresponding lobe. (See also page 402.)

Case 21: *Bronchitis ulcerosa* of the left lower bronchus with acinous foci in this lobe; we found also the Ghon focus in the same lobe.

Case 29: Deep ulceration (without perforation) of a large bronchus of the left lower lobe with the formation of an enormous caseated focus with central ulceration in this lobe. The Ghon focus was found on the other side in the lower lobe; it was active.

Case 39: Deep ulceration of the right main bronchus without perforation. Caseous pneumonia of the right upper lobe. The child died of a purulent and tuberculous peritonitis, the result of a perforation of tuberculous ulcers in the lower ileum.

Case 40: Deep ulcerations with perforations of the right main bronchus, leading directly to a pulmonary cavity situated in the upper third of the right upper lobe (primary cavity with a maximum diameter of 30 mm.). In the right upper and lower lobe we found several small softened cavities and numerous acinous and caseated foci.

(4) *Bronchogenous dissemination without bronchial lesions* (cases 3, 10, 17, 20 and 52). Doubtlessly there existed a bronchial lesion in these cases, but it was not found.

Case 3: Focus in the upper third of the left lower lobe and numerous bronchogenous foci in the rest of this lobe. In the upper lobe there were few acinous foci.

Case 10: Focus in the lower third of the right upper lobe, caseous pneumonia throughout the rest of the lobe.

Case 17: Numerous acinous foci in all pulmonary lobes, in a primary infection of a 10 year old girl. Also very intense hematogenous dissemination.

Case 20: Caseous pneumonia of both upper lobes in a primary infection of a 9 year old girl.

Case 52: Numerous acinous foci in all pulmonary lobes in the course of a cavernous phthisis in an 11 year old girl.

Intestinal lesions were found in all cases except cases 5, 20, 21 and 40, in spite of serious destruction of the bronchial mucosa found in the latter case. But we have to emphasize the great importance of bronchial tuberculosis for the development of intestinal ulcers. This is impressingly shown by our statistics, which show that in group A there were only 38 per cent intestinal foci, whereas in group B, with multiple bronchial lesions, there were 76.5 per cent.

G. SELECTIVE HEMATOGENOUS DISSEMINATION, ESPECIALLY TO THE LEPTOMENINGX IN CONNECTION WITH TYPICAL LYMPHOGLANDULAR EXACERBATION

Case 16: The primary focus was found in the right lower lobe near the base; it was fibrous, with the centre already calcified and about the size of a small pea. A lower right tracheobronchial lymph node contained a small caseated focus and several small calcified foci and miliary tubercles. The only hematogenous manifestation found was osteitis of the atlas and the epistropheus with complete destruction of the body of these vertebrae. The *dens epistrophei* was found completely severed from its base and hanging over the dura mater. We also found a cerebrospinal tuberculous meningitis with exudation and tubercles in the usual places. Because of the absence of miliary tubercles in the lung, liver and spleen one could also suppose a direct infection of the meninges from the vertebrae, a rare but not unknown condition. This latter possibility is supported by the finding of an isolated tuberculous pachymeningitis of the cervico-occipital region.

I. PRIMARY CASEATED COMPLEX IN ACTIVE STAGE WITH ISOLATED HEMATOGENOUS TUBERCLES

Case 45: An 11 year old boy with a relatively old caseated, pea-sized focus with central calcification, situated 1 cm. below the pleura near the base of the right lower lobe. The lower right tracheobronchial lymph nodes showed tuberculous hyperplasia and a few calcified foci. The right paratracheal lymph nodes showed tuberculous hyperplasia. In the lungs we found a few miliary tubercles. On sectioning the lungs no large recent or old foci were found, except the Ghon focus. But we found a tuberculous ulcerative laryngitis with complete destruction of the upper right chord and partial destruction of the left and lentil-sized ulcerations on the mucosa of the anterior wall of the larynx immediately below the inferior chords. In the intestine we found no ulcerative lesions. No macroscopic or microscopic lesions were found in the liver and spleen. From the pathogenetic point of view this is a rare case. In the first place, laryngeal tuberculosis is found very infrequently in children, probably because of the rapid evolution of their tuberculosis. Second, it seems to us undoubtedly one of the exceptional cases, confirmed by anatomical examination, of purely hematogenous laryngitis with a complete lack of major lesions of the lung. It seems impossible to blame the primary focus itself for this laryngeal infection, because of the lack of any indication of a cavitory process in the area of the focus. The small size of this focus with no cicatrization in its surroundings does not suggest the presence of a cicatrized cavity. Summarily this is an extraordinary case of hematogenous tuberculous laryngitis in a child of 11 years.

Clinically, the diagnosis of hematogenous tuberculous laryngitis is made with relative frequency in cases of hematogenous dissemination where the larynx is included and a pulmonary cavitory image is missing (Cohen (14), Donelly (15), Charlier (47), Stevenson (16)). But anatomically these cases are very scant and in our experience this is the only case. This child's death was caused by an intense rheumatic endo- and myocarditis.

Hematogenous laryngitis is so rare that in the current text-books it is only referred to very shortly.

J. PRIMARY FIBROUS CHEESY COMPLEX (CLOSED)

Cases 14, 18, 19, 43, 46, 47, 50 and 51.

Out of these 8 cases, there is only one that does not exactly correspond to the title. This is case 19, where we found a focus still caseous, but without any hematogenous complications. Cases 14, 18, 47 and 51 had a closed complex with cheesy-fibrous foci and lymph nodes; cases 43, 46 and 50 showed complete calcification. Five died of epidemic meningitis (nos. 14, 18, 19, 43 and 51), case 50 of otogenous meningitis, case 46 of typhoid fever and case 47 of uremia (pyelonephritis). We can say that the outbreak of epidemic meningitis notably diminishes the relative number of fatal tuberculosis which in normal years would probably reach 90 per cent of all tuberculosis autopsies.

L. PRIMARY CALCIFIED PULMONARY FOCUS WITHOUT LYMPH NODE CHANGES

Our case does not correspond exactly to the title used by Terplan (1).

Case 33: A 2 year old girl with a lentil-size focus in the right middle lobe. This focus was yellow, indicating recent caseation, and it was well demarcated from the surrounding normal tissue. Macroscopically, infected lymph nodes were not found, although all respective nodal groups were sectioned; neither did the histological examination of these lymph nodes disclose any tubercles. The examination of the focus showed a picture of pneumonia with intense desquamation of the alveolar epithelium and many large cells of varying shapes with large and clear nuclei in the alveoli. We found lymphocytes in large numbers, especially in the interstitial tissue, while in the alveoli there were more polynuclear cells. Caseation and giant or epithelioid cells were not observed anywhere, but we found a certain fibrinous exudation colored intensely pink with hematoxylin-eosin. No tubercle bacilli were found in sections. Neither did staining with Sudan III reveal the presence of fat (to explain the yellow coloring of the focus). We think there is a probability of this being a very recent primary tuberculous focus without infection of lymph nodes, such as have been described by Zarfi (25), Ghon and associates (24). We realize that the failure of demonstrating tubercle bacilli might indicate that this is not a primary focus. But at that times we had great difficulties in getting proper staining materials and parallel examinations of obviously tuberculous tissues gave equally negative results. This leads us to think that, in spite of all difficulties, this is a tuberculous focus. We present the following reasons: (1) its subpleural localization, and its circumscribed shape and the yellow coloring of the focus; (2) the delimitation which also shows in the histological examination, the lack of fats and the morphological picture itself of a pneumonic circumscribed focus with grave cellular alteration, fibrinous and cellular exudation in a place so circumscribed, without any bronchitis and peribronchitis, as it is generally observed in cases of bronchopneumonic nonspecific foci in childhood.

P. INTESTINAL TUBERCULOSIS WITH CASEATED MESENTERIC LYMPH NODES

In case 1 we found a very small flat ulcer situated in the ileum about 9 cm. above the ileocecal valve; its margins were only slightly elevated and its size was that of half a lentil. The bottom seemed red and gave the impression of the presence of small tubercles, especially near the margin of the ulcer. We found a completely caseated pea-sized lymph node adherent to the serosa, and, also in the ileocecal region, we found various partially caseated smaller lymph nodes. The lungs, liver, spleen and kidneys were examined macroscopically and some sections also histologically: there was no tuberculosis. The histological examination of the focus and lymph nodes gave the usual picture of an erosive intestinal tuberculosis with several miliary productive tubercles in the neighboring submucosa and the erosion itself was covered by pseudomembranes, constituted by necrotic masses and fibrin. The lymph nodes examined showed typical caseous tuberculosis. This child died of bronchopneumonia.

Case 20: The other case of a primary intestinal focus shows a cicatrizing erosion in the lower ileum with complete caseation of the local lymph nodes; the largest was 30 x 11 x 18 mm. Animal inoculation of one of the lymph nodes and a simultaneous culture yielded, as in case 1, tubercle bacilli of the human type. This child died of *endocarditis lenta*. As we already have said in the introduction, we connect the low number of intestinal infections with the scant consumption of milk.

DISCUSSION

In our material, 78.6 per cent of the foci were found in different stages of caseation, and 89.1 per cent, respectively, if we consider only the cases where tuberculosis was the cause of death. This number is higher than that of Lange (10) who found 77 per cent caseated foci in a material in which 83 per cent died of tuberculosis. (Naturally these comparisons are greatly influenced by the children's age, since in small children more caseated foci are found than in older children.)

In our material 5.3 per cent of the total and 6.4 per cent, respectively, of the cases that died of tuberculosis had multiple foci. These percentages are very similar to those of Ghon and Winternitz (6) (6.2 per cent) Lange (10) (7.1 per cent), Blumenberg (11) (8.7 per cent) and Ickert (20) (9.4 per cent), while Puhl (9) found 13 per cent and Terplan (1), among cases that died of tuberculosis, 17.4 per cent. One could well suppose that Terplan's material shows the real proportion, considering his use of radiological examinations.

The primary cavity, according to some authors (Auerbach cit. by (1)), is only produced shortly before death; this opinion is different from Ghon's (6), Terplan's (1) and Huebschmann's (12), and neither do we agree with it. So as to get a certain clarity and uniformity we should distinguish the proper primary cavity from the central liquefaction found in many primary foci. Naturally, the primary cavity is the final stage of a process which starts with caseation, softening and which finishes by the expulsion of necrotized masses. But even from the clinical point of view, the liquefaction without expulsion will probably not give the same radiological image; therefore the difference between central liquefaction and a real cavity has also a practical importance.

We do not want to create a substantial difference between central liquefaction and a cavity; we only want to emphasize the presence of a gradual difference between the two processes. Among 191 cases of progression foci Ghon (21) found 89 cases with cavities (46 per cent), Blumenberg (11) found 34 per cent, Loeschke (cit. 23) 25 per cent, Terplan (1) 20 per cent and Lange (10) 14 per cent. In our 36 cases of progressive foci we found 11 partially or completely caseated with central liquefaction and 8 with large cavities, that is, a total of 53 per cent, average higher than Ghon's, in spite of the fact that the latter's material consisted almost exclusively of babies under one year of age. This circumstance by itself raises the number of primary cavities, which are in direct relation to the children's age. This shows an impressive comparison to our group A material. The average of the children's age in this group was 4 years, the age of all 6 cases with liquefaction, one year. In other words, of the 26 children with hematogenous dissemination in group A, 2 were under one year of age (both with primary cavities), 8 between one and 2 years (4 of these with primary cavities) and 16 over 2 years with no primary cavities.

Table 6 from our material shows that the degree of softening also depends on age. With increasing age the danger of formation of a large cavity (primary

TABLE 6

Relation between age and development of the Ghon focus (groups A and B)

0-1 year	number: 4	cavities: 3	central liquefaction: 1
1-2 years	number: 11	cavities: 4	central liquefaction: 2
2-15 years	number: 29	cavity: 1	central liquefaction: 6

!!) apparently decreases considerably. The circumstance of finding in group B (combined hematogenous and bronchogenous dissemination) older children, in the first place, points to the well known fact that during the first month of life hematogenous dissemination is so early and intense that it does not even allow the development of bronchogenous tuberculosis, that is, the child rapidly dies of miliary tuberculosis. The great frequency of liquefaction and formation of cavities in our cases is so excessive, when compared to material like Terplan's (1), Loeschke's (23), Blumenberg's (11) etc., that it seems indispensable to try to find an explanation. In an interesting study, Mayer and Rappaport (22) present the theory of the development of tuberculous infection in relation to the epidemiological state of the population as shown in table 7.

From facts already explained in the introduction, we can deduce that Chile, in spite of its very high morbidity and mortality rate from tuberculosis, is yet distant from the apex of its tuberculization. Therefore we can count on *very low resistance* and an *acute development* of the disease, according to the first epidemiological stage. The primary cavities were frequently very large: the largest occupied two-thirds of the corresponding lobe (case 49); another one measured 5 x 2 cm. in a child of only 14 months (case 24). In 5 children the largest diameter of the primary cavity was about 3 to 3.5 cm. (cases 11, 13, 8, 4

and 48). Only one was bean-sized (case 10). In our material there are many more softened and cavernous foci on the right side than on the left. For example, in no less than 5 out of 9 cases the cavities were situated in the right upper lobe, 3 in the other right lobes and only one cavity was in the left lower lobe. Liquefaction of bronchogenous secondary foci seems unusual in children; Ghon mentions it twice, Terplan (1) only once; we have observed it in a series of cases (9, 29, 40, 48 and 52).

We also attach importance to the great proportion of the female sex in cases of liquefaction of the primary focus (13 girls and 4 boys), while the total of

TABLE 7

Development of tuberculous infection in relation to epidemiology (Mayer and Rappaport)

TUBERCULIZATION	UPGRADE	PEAK	DOWNGRADE
Community.....	Virgin	Tuberculized fully	Detuberculization
Mortality.....	Rising	Highest	Declining steadily
Morbidity.....	Rising	Highest	Declining steadily
Resistance.....	Low but rising	High	Beginning to decline
Allergy.....	Low but rising	High, prevalent and permanent	Declining
Contact.....	Increasing	Wide-spread and severe	Declining
Infection.....	Rising incidence	Prevalent before adult age reached	Declining, particularly before adult age
Reinfection.....	None	None, hardly ever before middle age	Rising throughout adult age
Disease.....	Acute and sub-acute generalized forms	Chronic endogenous phthisis and chronic hematogenous forms	Chronic exogenous phthisis
Latency.....	Infrequent, short	Prevalent and long between primary and chronic pulmonary tuberculosis between bouts of hematogenous dissemination	Declining and shortening between primary and chronic pulmonary tuberculosis

fatal cases shows a proportion of 25 girls to 20 boys. In another place we will go back to the importance of sex in the development of tuberculosis.

We have observed a cavernous tuberculosis of the adult type in the presence of a caseous Ghon focus in an 11 year old girl (case 52), in whom we found immense cavities in all five lobes. The largest was the size of a hen's egg. The Ghon focus was slightly ulcerated in the centre but it had a cheesy-fibrous capsule.

We observed a tuberculous ulcerated tonsillitis without bronchial tuberculosis and without a pulmonary cavity (case 30). We do not think we overlooked a bronchial ulceration, neither did we find tuberculous ulcers in the intestine. We consider this case an example of hematogenous infection of the tonsils, as in case 45 where we classed the pathogenesis of tuberculous laryngitis as hematogenous, seeing it lacked pulmonary and bronchial exudative foci. Naturally,

these cases are exceptional and we fully agree with other authors who say that the tuberculous infection of the tonsils, the larynx and the intestine is generally intracanalicular and depends either on an exudative cavitary pulmonary process or on an ulcerated bronchial process.

We would like to add a few words concerning the diagnosis of whooping cough in tuberculous children. In old and modern texts we frequently find that pertussis is very important as a forerunner and placemaker of a tuberculous generalization either of the hematogenous or bronchogenic type. In our material we have observed the diagnosis of pertussis in a large number and we feel that undoubtedly bronchial tuberculosis, bronchial alterations caused by lymph node compression and other factors, such as the stasis of bronchial exudation etc., can cause a clinical syndrome with attacks very similar to pertussis (Simon and Redeker (23)). These authors say, "... not very rarely we observe this confusion," meaning the confusion between whooping cough and the symptomatic cough of tuberculosis. Very impressive is example no. 22 of these authors: "... the case of a 3 year old boy who, a year and half ago, had been infected by his mother. During several days the cough shows the typical characteristics of whooping cough of certain intensity: fits at the beginning, facial cyanosis, grave reprise, vomiting and suffocation. The fits of coughing repeated themselves several times every day and were so similar to whooping cough fits that it was impossible to convince the personnel of the clinic that this was not the case, although the personnel had had ample experience with sick children. Neither in the sanatorium nor at the child's home, where he had a little sister of a year and a half, was there a case of pertussis. On the contrary, the X-ray photograph and the existence of a fistulated cervical lymph node with several phlyctenulae support the diagnosis of a lymph node and bronchial tuberculosis."

We do not consider the histological examination of the lungs specific enough to diagnose pertussis. Confirming other author's descriptions, we have frequently found bronchitis and peribronchitis in these cases but it is our experience on abundant and selected children material that the greater part of infantile pulmonary disease is produced under a similar picture. We have frequently seen this in paravertebral bronchopneumonia, in current pneumococcic bronchopneumonia, in cases with bronchiectasis, etc.

According to the 1937 statistics, Chile heads the whooping cough mortality. No less than 20.2 in 100,000 die of pertussis in Chile. This contrasts with the average of New Zealand (0.9), Sweden (1.6), U. S. A. (3.9), England (4.3), Uruguay (5.0), etc. We think that many, if not most cases that are listed as victims of whooping cough in Chilean statistics, in reality died of tuberculosis, since bacteriological diagnosis of pertussis is not even practiced in all hospitals and is practically unknown outside these. We selected at random from our material cases 4, 11, 54 and 55, all sent in with a diagnosis of pertussis, so as to prove our opinion.

Case 4: Recent Ghon focus with large masses of caseated lymph nodes, with compression of numerous bronchi. Many atelectatic foci had formed in all pulmonary lobes. More-

over, a bilateral hydrothorax (200 cc.) and bronchiectasis, especially in the right lower lobe, were found.

Case 11: Primary cavity, 2 cm. in diameter, with a perforation into the pleura and right pyopneumothorax. Right pleuropericarditis in organization.

Case 54: Large, pea-sized tuberculous focus, completely caseated. Large plum-sized bundles of caseated lymph nodes, compressing several bronchi. Besides, numerous pulmonary miliary tubercles.

Case 55: Without referring to the well known picture of the primary complex with large lymph node masses, we found a bronchial perforation of an ulcerated lymph node next to the right middle bronchus. In this case we found a nearly complete atelectasis of the right middle lobe and a hydrothorax, hydropericardium and an apparently tuberculous destructive laryngitis.

These 4 cases show clearly, in our opinion, that the clinical diagnosis of whooping cough cannot be maintained in cases of cough in children if rigorous examinations, especially cultures, are not made. From this we have to deduce that a large number of cases which, according to the statistics, die of whooping cough should be added to those dead of tuberculosis. This is surely the most logical explanation for such a high whooping cough mortality rate for which there seems no other cause.

Cases described as epituberculosis (Eliasberg (30)) are the ones with radiographic shadows in one or more pulmonary lobes. Usually one finds an anatomical substrate in the form of an atelectasis caused by a compression of the bronchi by lymph nodes which generally belong to a primary complex, or by a rupture of lymph nodes into the bronchial lumen or by endobronchial complications. (References 26 to 41.) Blatt, Simon and Redeker, etc. still maintain the concept of massive benign perifocal inflammation as an anatomical substrate; we consider this mistaken.

We agree mainly with the expert opinions of Roessle, Terplan, etc., but we have to add that we consider the syndrome of epituberculosis as infrequent; we doubt that prognosis is as absolutely benign as suggested by some clinics; and lastly we believe that the mechanism of production of atelectasis is more complicated than it seems at first sight. As for the prognosis, a study of the cases in the literature and our own (small) experience teach us that the atelectatic lung participates in tuberculous dissemination, whether hematogenous or bronchogenic, so that the evolution of the atelectatic lobe may depend only on the development of the basic pulmonary process which makes us emphasize the possibility of stating that not every epituberculosis has a benign prognosis. For example Terplan, in 3 out of 5 cases of epituberculosis, describes bronchial tuberculous lesions in the atelectatic lobe, so that undoubtedly bronchogenic foci would have formed in these cases.

As for the mechanism of production, according to our experience, the mere compression of the principal bronchi generally does not produce atelectasis, apparently because of the great rigidity of the main bronchi. We have seen

atelectasis in compressions of the minor bronchi by cascated lymph node masses, not very large, but always accompanied by an intense specific endobronchial exudation of catarrhal or mucopurulent nature. This is not the place to discuss whether the presence of endobronchial exudate is cause or consequence of pulmonary atelectasis. We consider it a consequence of bronchial compression; a stagnation of the exudate takes place and this automatically produces an infection of the stagnant exudate and a rapid increase of secretion; and this, even if does not actually produce atelectasis, at least helps to produce it. Also in cases where atelectasis is produced exclusively, by endobronchial processes, such as tuberculous ulcers of the bronchial mucosa, we always see a large quantity of exudation which, as in the former example, we consider indispensable for the provocation of atelectasia. Some experiences which we published with Meneghello and Peña also shed some light on this point (13). They refer to the effects of aspiration of this exudation which rapidly changes the radiological picture; the formerly atelectatic lobe now acquires its normal image. According to our opinion, one could define epituberculosis as an infrequent syndrome which is produced generally in children and is related to primary tuberculous infection, having as an anatomical substrate an atelectasis which, in its turn, is produced either by outside compression without specific endobronchial lesions (Rocssle's "pure" cases), but accompanied by an abundant secretion, caused by stagnation of normal secretion; or which is caused by endobronchial processes, such as ruptures of lymph nodes into the bronchial lumen, bronchial ulcers etc., all accompanied by abundant bronchial exudation. Our cases clearly prove what we have said.

Case 4: A 4½ year old boy. Nearly complete atelectasis of the right middle lobe with many miliary tubercles in the parenchyma of the affected lobe. Most of the large and small bronchi of this lobe were obstructed by mucopurulent exudate which was microscopically nonspecific. Some bronchi also showed specific lesions with small specific acinous foci. Compression had developed in the interlobular septa where immense lymph nodes, belonging to the primary complex (the focus was found in the left lower lobe), compressed the right middle bronchus. In the left lower lobe we found some acinous foci and wide-spread atelectasis. The histological examination revealed tuberculous endobronchitis of numerous completely covered small bronchi, most of them with polynuclear exudate. Without examining the cause of the infection of the bronchial mucosa, it shows us in this case: (1) atelectasis of a whole lobe (right middle) caused by compression and a grave specific, mucopurulent endobronchitis and (2) a tuberculous endobronchitis of the left lower lobe, which, with its abundant purulent exudate, is sufficient to produce itself (without bronchial compression) an atelectatic zone. As a consequence of tuberculous bronchitis in the two mentioned lobes, acinous foci were produced; we want to emphasize this in contrast to the absolute benignity of epituberculosis proclaimed by some authors.

Case 55: A 4 year old girl with a completely ulcerated and caseated focus in the right middle lobe. Regional caseated lymph nodes produce a perforation of the right middle bronchus with large masses of exudate in the lumen. The right middle lobe consequently shows a nearly complete atelectasis and acinous foci, while the other pulmonary lobes only show signs of hematogenous dissemination. The presence of a sero-hemorrhagic

pleuritis (100 cc.) may also have contributed to the formation of atelectasis. This case (already described in the chapter referring to pertussis), like case 4, shows that pulmonary atelectasis is produced by many causes, not only by one. Case 4 could be interpreted as "pure" epituberculosis (Roessle), since the principal cause is a compression from the outside (only microscopically we found a tuberculous endobronchitis of small bronchi, independent of bronchial compression). Case 55 is an example of epituberculosis by specific exudate, produced chiefly by a rupture of softened and caseated lymph nodes into the bronchial lumen.

In our experiences we find more cases of lymph node ruptures into bronchial lumina without atelectatic lesions. The easiest explanation would be that atelectasis is a very short stage which rapidly disappears if some obstacles are removed, but we do not know whether this explanation is correct and satisfactory in all cases.

We also want to say a few words about meningitis found in our cases, because in a future study with Meneghello we will describe *in extenso* our observations

TABLE 8

Relation between age and tuberculous meningitis in hematogenous diffuse generalization in our material (45 cases)

	WITHOUT MENINGITIS	MENINGITIS	TUBERCULOMA WITHOUT MENINGITIS
0-12 months.....	2	2	
12-24 months.....	3	7	2
2-6 years.....	11	5	1
6-10 years.....	3	5	
10-14 years.....	3	1	
Total.....	22	20	3

in 30 cases. In our material a relatively small number of meningitis cases attracts our attention. Terplan (1) observed meningitis in all cases with hematogenous generalization; we only found it in 20 out of 45 cases with hematogenous diffuse generalization (44.4 per cent). Probably this fact is influenced by the children's age and by the malnutrition and lack of resistance found in our material which lead to the children's death before meningitis is developed.

In table 8, our 45 cases with hematogenous dissemination are presented.

Another comparison between Huebschmann's (12), Terplan's (1) and our material yields the results presented in table 9.

Out of our 20 cases, 12 were girls with an average age of 3.7 years and 8 boys with an average age of 6 years. Levinson (42) in his 899 cases of tuberculous meningitis had 57 per cent males (574 cases) and 43 per cent females (385 cases).

Meningitis developed as a consequence of early dissemination, that is, in immediate relation to primary infection, in 13 cases: 11, 13, 17, 21, 27, 34, 35, 37, 38, 42, 48, 56 and 57. In the 7 remaining cases we found a completely calcified focus four times (16, 36, 44, 53), a cheesy fibrous Ghon focus with a calcified

centre once (25) and in 2 cases the focus was not found (6, 26). In the cases with a calcified focus we found the following nodal lesions.

Case 16: Regional lymph nodes with calcified foci, the larger ones were caseated and had miliary and confluent tuberculous foci.

Case 36: Tracheobronchial lymph nodes were calcified; we found cheesy-fibrous foci in the paratracheal lymph nodes and in the venous angle and small grayish nodules in hyperplastic lymph nodes.

Case 44: Complete calcification of the broncho-mediastinal lymph nodes without active foci.

TABLE 9

Comparison of relation between age and meningitis in postmortem material of Huebschmann (Düsseldorf, Germany), Terplan (Buffalo, U. S. A.) and Schwarz (Santiago, Chile) in hematogenous generalized forms

	TOTAL NUMBER OF CASES	HEMATOGENOUS GENERALIZATION WITH MENINGITIS	HEMATOGENOUS GENERALIZATION WITHOUT MENINGITIS	MENINGITIS WITHOUT DIFFUSE HEMATOGENOUS GENERALIZATION
0-12 months				
Huebschmann.....	25	76%	16%	8%
Terplan.....	2	100%	0	0
Schwarz.....	4	50%	50%	0
1-5 years				
Huebschmann.....	89	75.2%	6.6%	17.9%
Terplan.....	17	88.2%	0	11.8%
Schwarz.....	26	42.4%	57.6%	0
6-10 years				
Huebschmann.....	26	88%	0	12%
Terplan.....	1	100%	0	0
Schwarz.....	11	45%	45%	10%

Case 53: Tuberculous hyperplasia of the paratracheal lymph nodes and in the venous angle; the hilar nodes were calcified.

Cases 25 and 26 had, beside their calcified foci, caseous zones in the lymph nodes of the venous angle.

Therefore we can say that, although tuberculous meningitis is frequently produced in the stage of early generalization, there are many cases where it is a consequence of a reactivation of the tuberculous process in the lymph nodes of the primary complex. This statement openly contradicts the opinion of Simon and Redeker (23) who, quoting Engel, say: "... a tardy meningitis is an anomalous event. Out of 36 cases of meningitis in children over 3 years Engel has seen only 2 cases proceeding from medium-aged foci."

As for the presence of tuberculomata in cases of tuberculous meningitis, due to circumstances beyond our control, it was impossible to obtain adequate

fixation of the brain before slicing, so that the sections made were relatively thick and incomplete in the few cases where it was possible to cut the brain. In spite of these adverse circumstances we found in the 13 cases in which the brain was sectioned 7 examples of tuberculomata, generally in the cortical substance or immediately underneath it (cases 17, 25, 27, 35, 37, 48 and 53). Besides, in 2 cases we found meningeal tuberculomata, apparently of the arachnoid, which certainly had no relation to the brain substance itself (cases 11 and 44). We believe that the tuberculoma has a great importance in the formation of meningitis (according to Rich (45)), and this opinion is strengthened by the finding of 3 cases with tuberculomata without meningitis. (One of the chief arguments against the importance of the intima tubercle of Weigert in cases of miliary tuberculosis is, according to Huebschmann (12), that it is never found unless miliary tuberculosis has already attained the stage of complete development. Comparing this to tuberculous meningitis we could say that cortical tuberculomata may easily be the cause of meningitis as they are also found in cases with no meningitis.

In several cases we have observed a group of miliary tubercles around the tuberculoma, in others there were none. This gives us the impression that the presence of tubercles around cortical tuberculomata depends chiefly on the lesion of the dura mater. In cases of pachymeningitis due to tuberculomata the perifocal spread was also evident in the leptomeninx.

The relation between tuberculous ostitis and meningitis can be characterized as follows: tuberculous destruction of the two first cervical vertebrae seems responsible only in case 16 for the meningeal infection; we found a circumscribed pachymeningitis with many small miliary nodules in the region of the medulla oblongata and tuberculous cerebrospinal meningitis. In this case there was an absolute lack of other localization of hematogenous dissemination.

In some cases ostitis was certainly older than meningitis, such as in case 44, where one year before death an osteoplastic operation of the spinal column had been performed, so as to prevent its complete destruction. During the autopsy we found a small tuberculoma in the leptomeninx which apparently developed in another phase of hematogenous dissemination; we consider it the cause of meningitis in this case. Among our 45 progressive cases we have observed 5 cases with tuberculous osseous lesions (cases 5, 7, 16, 25 and 44), all with vertebral foci, excepting case 25 where we found coxo-femoral arthritis. In many text-books it is described practically as a law that ostitis is the only extrapulmonary tuberculous localization. In case 5 we observed, apart from a miliary spread in all the organs, tuberculous peritonitis and pleuritis; in case 7 several miliary tubercles in the lung; in case 16 only a calcified primary complex; in case 25, apart from hematogenous dissemination, intestinal ulcers (hematogenous?); and in case 44 hematogenous dissemination and a tuberculous abscess in the left psoas. It is noteworthy that 4 cases had lesions either meningeal (16, 25, 44) or cerebral (4) or combined (25); this shows the importance that osseous foci have for hematogenous dissemination, as the majority of osseous foci are older than the final hematogenous generalization (Kremer (43) Harms and Merker (44)).

In case 20 we found near the pea-sized focus a thrombosed vein with a diameter of about 4 mm.; in case 54 we observed near the focus thrombosis and apparent caseation of the wall of a vein. The results of histological examination were, in both cases, large caseated tubercles in the walls of the respective veins. The finding of this lesion of the veins made us think of the possibility of a relation to generalization, and the histological picture of recent foci confirmed this opinion of which we will give an account another time.

In case 54, examination of the spleen revealed the same vascular lesions as in the lung, that is, abundant tubercles in the intima of numerous vessels with or without ulceration. This case seems very instructive as an illustration on the immense difficulty of forming an opinion of the formal pathogenesis of hematogenous generalization. The frequent circulation of tubercle bacilli in the blood, in many cases of progressive tuberculosis, seems to be proved (Liebermeister, Löwenstein, Huebschmann (lit.)). Huebschmann (12) arrives at the same conclusion from the general state of the patient. Lately we have seen several examples of completely calcified latent foci where the deterioration of the general state influenced the reactivation of the lymph nodes of the primary complex. We are convinced that such reactivation of tuberculous processes occurs and that it can be proved beyond doubt by anatomical evidence. These lymph node reactivations lead, specially in the adult, to generalization; in children and in people with recent foci, we believe that bacilli have many opportunities to enter small or larger vessels in the primary focus or immediately around it, by lympho-hematogenous propagation in relation to the focus or the caseated lymph nodes of the primary complex and by actual rupture of caseated masses through the vascular walls in the foci or in lymph nodes. We see no possibility of finding in every case the exact origin of bacillema, specially since in every case there are probably several or even many regions of blood-stream invasion. From the morphological point of view it seems certain that the entry of bacilli into the circulation can take place (1) in the primary focus, (2) in any caseated lymph node, (3) in any pulmonary focus, specially when caseated (4) it may take place in combined lympho-hematic form, depending on foci and lymph nodes and (5) naturally in any extrapulmonary focus. It seems unjustified to look for the portal of entry chiefly or exclusively in the venous angle, even if one finds a large caseated lymph node next to the vena cava superior, and frequently visible through the venous wall to which it usually adheres. We do not in any way want to deny the importance of the lymph nodes of the venous angle. Ghon and his pupils (46, 1) have proved their significance. We only want to insist on the possibility, of whose frequency we know very little, that bacilli may enter into the circulation in other places, emphasizing the importance of the primary focus itself. We do not know the reason why foci often cicatrize and why in other cases there occurs a propagation of the tuberculous process; we cannot expect to elucidate this by morphological methods, nor can we know why the bacilli, while circulating in the blood-stream damage only certain organs and never attack all organs in the same form. (Table 10 presents a final summary of the distribution of tuberculous lesions observed in our 45 cases of tuberculosis in children.)

TABLE 10

Forty-five cases in which tuberculosis with hematogenous dissemination was the cause of death; localization of macroscopic findings

GROUP	NUMBER	AGE	SEX	TUBERCLES IN LUNGS	MENINGITIS	TUBERCLES IN					INTES-TINAL ULCERS	ADDITIONAL FINDINGS OF TUBERCULOSIS
						Brain	Liver	Spleen	Kidney	Perito-neum		
A ₁	11	7 m	m	++++	++++	-	++	+++	+	-	++	Meningeal tuberculoma
	12	6 y	f	++++	-	-	+++	+++	+++	-	-	Urinary bladder
	13	18 m	f	+	++++	-	+++	+++	-	-	+++	Pachypleuritis
	25	3 y	m	++	++++	+	+++	++	+	-	++	Coxo-femoral osteo-arthritis
	27	15 m	m	-	++++	+	++	+	-	-	++	Discrete perifocal spread (lymphogenous)
	28	5 y	m	-	-	-	+++	++	+	-	-	
	30	2 y	m	+	-	-	++	+++	+	+++	-	Ulcerous tonsillitis
	31	2 y	f	+	-	-	++	+	-	-	-	
	32	7 y	m	(+)	-	-	++	+++	-	-	-	
	34	9 y	f	+	++++	-	+	+	+	-	++	
	35	3 y	f	++	++++	+	+++	+++	+++	+++	-	
	38	15 m	f	++	++++	-	++	+++	+	-	-	
	41	2 y	m	++	-	-	++	++	-	-	-	
	42	12 y	m	+	++++	-	+	++	+	-	+	
	54	13 m	m	++++	-	-	+++	+++	++	-	-	
	56	10 y	m	++++	++++	-	+	+++	(+)	-	-	
	57	15 m	m	(+)	++++	-	+	+	-	-	-	
A ₂	2	10 y	m	-	-	-	++	++	+	-	-	Thyroidea
	6	18 m	m	+++	+++	-	+++	+++	+++	-	+++	
	26	24 m	f	++	+++	-	+	+	-	-	-	
A ₃	36	6 y	f	++	+++	-	++	+++	-	+++	+++	Pachypleuritis Ostitis; meningeal tuberculoma
	44	10 y	m	+	+++	-	+++	+	++	-	-	
	53	2 y	f	+	+++	+	++	++	-	-	-	
A ₄	7	6 y	f	+	-	+	-	-	-	-	-	Ostitis
	8	16 m	m	+++	-	-	++	+	-	-	+++	
	23	7 m	f	++	-	-	+++	+++	-	-	++	
B	3	4 y	m	+++	-	-	++	+	-	-	++	Ostitis, adrenals, pachypleuritis Polyserositis Adrenals Urinary bladder
	4	4 y	m	+++	-	-	+++	++	++	-	++	
	5	12 y	m	++	-	-	+++	(+)	+	+++	-	
	9	3 y	f	++	-	-	+++	+++	+++	-	+++	
	10	18 m	f	+	-	-	++	++	+	+++	+++	
	15	20 m	m	++	-	+	+++	+++	+	-	?	
	17	10 y	f	++	+++	+	+++	+++	+++	-	+++	
	20	9 y	f	+++	-	-	++	+++	+++	-	-	
	21	13 m	f	-	+++	-	+	+++	-	-	-	
	24	14 m	f	++	-	+	++	+	+	-	+++	

TABLE 10—Continued

GROUP	NUMBER	AGE	SEX	TUBERCLES IN LUNGS	MENINGITIS	TUBERCLES IN					INTESTINAL ULCERS	ADDITIONAL FINDINGS OF TUBERCULOSIS
						Brain	Liver	Spleen	Kidney	Peritoneum		
B	29	14 y	f	+++	—	—	—	—	—	—	+++	
	37	6 y	f	+++	+++	+	+++	+++	+	+++	++	
	39	3 y	m	+	—	—	+	+++	—	+++	+++	
	40	4 y	f	+	—	—	—	—	—	—	—	
	48	7 m	f	+++	+++	+	+++	+++	+	—	++	
	49	9 m	f	++	—	—	+++	++	+	—	++	
	52	11 y	f	+++	—	—	+	(+)	—	—	++	Adrenals
	55	4 y	f	+++	—	—	+	++	+	—	++	Laryngitis
G	16	9 y	m	—	+++	—	—	—	—	—	—	Ostitis

SUMMARY

1. A comparison between anatomical material from Buffalo (U. S. A.) and Santiago (Chile) shows that the percentage of infected children and the death rate of tuberculosis are very much higher in Santiago.

2. The incidence of tuberculin-positive reactors is much higher in Chile than in U. S. A.

3. The rarity of intestinal foci in Santiago is explained by the insignificant consumption of milk, specially in the uncooked stage.

4. While in Buffalo most children, dead of tuberculosis, had only hematogenous generalization, in our material we frequently found bronchial spread combined with hematogenous dissemination.

5. Especially in this last group (group B) we found numerous Ghon foci with cavitation and with extensive involvement of the bronchial mucosa; we emphasize the great importance that bronchial foci hold for bronchogenic dissemination and intestinal (secondary) infection.

6. Tuberculous laryngitis in children—even in cases with large pulmonary cavities—is infrequent. Examples are presented of a case of hematogenous laryngitis and of a case with hematogenous tonsillitis, without exudative or cavitory pulmonary lesions.

7. Multiple Ghon foci were found only in 3 cases; we emphasize the diagnostic difficulty when multiple foci of similar appearance are found in the same lobe. It is chiefly the size of the primary focus that determines central liquefaction and the formation of a cavity. In this indirect way the size of the focus determines the evolution of the disease; a large, not ulcerated focus has, in our opinion, no other consequences than a small focus in the same circumstances. Only the formation of a primary cavity indicates a bad prognosis, not the size itself.

8. The distribution of cavitory Ghon foci greatly favors the right lung. (Out of 9 cavitory cases, 8 were found on the right side.)

9. The liquefaction of the focus depends apart from its size on the age of the child. The number of cases with primary cavities decreases rapidly after 2

years of age. The large number of ulcerations and cavities in our material is partially explained by epidemiological factors, as the curve of infection still ascends (53 per cent of the progressive foci were found to have cavitation).

10. The great importance of bacteriological diagnosis of whooping cough is discussed; many cases of "pertussis" are in reality either symptomatic cough of tuberculous processes such as bronchial compression or cavitary tuberculosis of the lung.

11. Two cases of atelectasis (epituberculosis) are presented; we emphasize the infrequency of this picture, the importance of accumulation of causes that produce atelectasis and the necessity of a careful prognosis of these cases, as in our (and other) material atelectasis is always accompanied by a tuberculous infection of the atelectatic lobe. The prognosis of "epituberculosis" will depend on the general evolution of tuberculosis and not only on the elimination of causes of atelectasis.

12. Bronchogenic dissemination is shown in 4 groups:

- (a) Perforation of bronchial wall by caseated lymph nodes.
- (b) Bronchial perforation related to pulmonary cavities.
- (c) Ulcerations of bronchial mucosa, with or without perforation.
- (d) Bronchogenic dissemination without a macroscopic involvement of the bronchial mucosa.

13. The importance of the Ghon focus in the formal pathogenesis of hematogenous dissemination is discussed. In 2 cases we have observed macroscopic lesions of large blood vessels with thrombosis near the Ghon focus. Microscopic lesions of the vessels are frequently found. The circulation of tubercle bacilli in the blood is admittedly frequent in all stages of progressive tuberculosis.

14. In our material girls are more seriously affected (without relation to puberty); out of 20 cases of tuberculous meningitis 12 were girls; out of 17 softened Ghon foci 13 were in girls; out of 18 cases of combined bronchogenic and hematogenous dissemination 13 were girls.

15. Tuberculous meningitis is generally observed in early hematogenous generalization; after the third year of age the frequency of meningitis diminishes.

16. We consider the presence of brain tuberculomata of great importance for the formal pathogenesis of tuberculous meningitis, because of:

- (a) The frequency of tuberculomata.
- (b) Finding of tuberculomata without meningitis.
- (c) Difference in the ages of meningeal nodules and in other organs.
- (d) Lack (nearly without exception) of miliary tubercles in the brain substance.

SUMARIO

1. Una comparación del material de autopsias entre Buffalo (USA) y Santiago (Chile) demuestra que la cifra de los niños infectados y la de los fallecidos de tuberculosis es mucho más alta en Santiago, lo que corresponde a hechos comprobados también con la estadística corriente de mortalidad.

2. Las cifras de tuberculinización en Chile son mucho más elevadas que en EE.UU.

3. Se explica la escasez de chancros intestinales en Santiago con el consumo insignificante de leche especialmente en forma cruda.

4. Mientras en Buffalo entre los niños muertos de tuberculosis la mayoría tenía únicamente generalización hematógena, en nuestro material la diseminación broncógena combinada con hematógena es frecuente.

5. Especialmente en este ultimo grupo se encontraron numerosos chancros primarios cavitarios y con gran compromiso de la mucosa bronquial por su vez acompañada casi sin excepción, por úlceras intestinales. Se subraya la gran importancia de focos en los bronquios para la diseminación broncógena y la infección intestinal (secundaria).

6. La laringitis tuberculosa en niños-también en casos con grandes cavernas pulmonares-es rara; se describe un caso de laringitis hematógena, faltando por completo lesiones exudativas o cavitarias en los pulmones. En iguales condiciones se da el ejemplo de una amigdalitis hematógena.

7. Chancros múltiples se encontraron en 3 casos; se destaca la dificultad diagnóstica de un chancre primario encontrándose focos múltiples de aspecto parecido en el mismo lóbulo. El tamaño del chancre primario determina en primer lugar la ulceración central y formación de una caverna. En esta forma indirecta determina el tamaño del chancre la evolución de la enfermedad; un chancre grande no ulcerado según nuestra opinión no debería tener otras consecuencias que un chancre pequeño en las mismas circunstancias. Solamente la formación de la caverna primaria desmejora el pronostico, no el tamaño mismo del chancre.

8. La distribución de los chancros cavitarios favorece mucho el pulmón derecho. (De los 9 casos cavitarios 8 se encontraron al lado derecho.)

9. El reblandecimiento del chancre depende fuera del tamaño de la edad del niño. El número de los casos con caverna primaria baja rápidamente después de los 2 años. El gran número de ulceraciones y cavernas en nuestro material se lo explicamos parcialmente por factores epidemiológicos, siendo la curva de infección todavía en aumento. (53% de los chancros evolutivos se encontraron reblandecidos.)

10. Se discute la gran importancia del diagnóstico bacteriológico de la pertussis; muchos casos de pertussis en realidad ya son tos sintomatica de procesos tuberculosos como tuberculosis o compresión de los bronquios, tuberculosis cavitaria del pulmón etc.

11. 2 casos de atelectasia pulmonar correspondientes al capitulo de epituberculosis se describen; se destaca la rareza del cuadro, se subraya la importancia de la acumulación de causas para la producción de tal atelectasia, y se hace hincapié en la necesidad de un pronóstico cauteloso de estos casos, siendo en nuestro y en el material de otros la atelectasia casi siempre acompañada con infección tuberculosa del lóbulo atelectasiado, de modo que el pronóstico dependerá de la evolución general de la tuberculosis y no solamente de la eliminación de las causas de la atelectasia.

12. Se presenta el compromiso bronquial en la diseminación broncógena en 4 grupos:

(a) Perforaciones de la pared bronquial por ganglios caseificados.

- (b) Perforaciones bronquiales relacionadas con cavernas pulmonares.
- (c) Ulceraciones de la mucosa bronquial sin o con perforación.
- (d) Diseminación broncogena sin compromiso macroscópico de la mucosa bronquial.

13. Se discute la patología formal de la generalización hematogena destacándose la importancia del chancre primario, donde ya macroscópicamente hemos visto en 2 casos el compromiso de grandes vasos sanguíneos y donde con frecuencia se descubren lesiones microscópicas. La circulación del bacilo de Koch en la sangre se admite como frecuente en todas etapas de una tuberculosis evolutiva.

14. El sexo femenino presenta en nuestro material las formas más graves; de los 20 casos con meningitis 12 fueron niñas, de los 17 chancros reblandecidos 13, de los 18 casos con diseminación broncogena y hematogena 13, etc.

15. La meningitis se ve generalmente como complicación de la diseminación precoz en el niño; disminuye el número de meningitis después del tercer año de la vida.

16. En favor de la gran importancia de tubérculos solitarios en la patogenia de la meningitis habla:

- (a) La presencia frecuente de tuberculomas.
- (b) El hallazgo de tuberculomas sin meningitis.
- (c) La diferencia entre la edad de los tubérculos en las meninges y en otros órganos.
- (d) La falta (casi sin excepción) de tubérculos miliares en la sustancia cerebral.

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DEGREE OF TUBERCULIN SENSITIVITY¹

Its Significance in Tuberculous Patients

ROBERT W. CLARKE

The purpose of this study was to determine whether any significance could be attributed to the severity or degree of sensitivity of the tuberculin reaction in patients in a tuberculosis sanatorium. The following points, therefore, were considered:

- 1: Relationship of absence of active tuberculous infection to the degree of tuberculin reaction.
- 2: Relationship of the duration of the disease, as determined from the patient's history, to the degree of tuberculin reaction.
- 3: Relationship of present or recent pleurisy with effusion to the degree of tuberculin reaction.
- 4: Relationship of the state of disease (minimal, moderately advanced and far advanced) to the degree of tuberculin reaction.

REVIEW OF THE LITERATURE

There is much controversy in the literature as to the significance of the degree of tuberculin sensitivity in the individual. Furcolow (1) stated that the quantitative differences in the degree of sensitivity to tuberculin appeared to bear an inverse relation to the severity of the tuberculous infection. He also stated that "the percentage of those who died within six months following the study was four times as great among the least sensitive to tuberculin as among the remainder."

Schwartz (2) found that "the degree of sensitivity of the graduate nurses was greater than that of the students but was somewhat less than that of a group of tuberculous patients who had been tested previously."

Colwell and Mills (3) found that, in dogs, impairment of general health, including severe tuberculosis, reduced sensitivity manifestations. On the other hand, Appel *et al.* (4) concluded from their series that "the evidence would indicate that no relationship existed between tuberculin sensitivity and prognosis."

Skavlem (8) concluded that repeated exposure keeps allergy high. He also states, "we must not overlook the fact that with the healing of the tuberculous lesions, allergy is lowered, and finally may disappear. It has been shown that the stronger the original reaction, the less frequently it disappears."

Clayson (5), using guinea pigs, noted that "at the local lesion, caseation takes place most readily in high degrees of allergy, and fibrosis most readily in low degrees of allergy. But the spread of lesions takes place most readily in low degrees of allergy and localization of lesions takes place in high degrees of allergy."

¹From the Barlow Sanatorium, Los Angeles, California, Howard W. Bosworth, Medical Director.

The variations of the degrees of allergy have been attributed to many and sundry causes. Mering (7) found no correlation between age or radiographic findings and sensitivity to tuberculin. Gomez (6) concluded that there was a variation of tuberculin sensitivity which could be correlated with the seasons of the year, the peaks of sensitivity being in June and December (winter and summer of the southern hemisphere).

From this brief review of the literature, it can be seen that no certainty exists as to the significance of the degree of tuberculin sensitivity. None of these authors took into account the relation of the duration of the infection in the individual to his tuberculin sensitivity, except Skavlem (8) who did note that, with the healing of the tuberculous lesions, allergy is lowered.

SOURCE OF MATERIAL

This study covers all patients admitted to Barlow Sanatorium from March, 1939 to March, 1944, a total of 338 patients. Each patient, when admitted, or within a few days of admission, was tuberculin tested by the Mantoux test. PPD tuberculin was used in all cases. This was made into such dilutions that four graded strengths could be used. The strengths were 1:10 first (.000,002 mg.), first (.000,02 mg.), 1:10 second (.0005 mg.) and second strength (.005 mg.); 1:10 first strength was always given as the initial test, and each succeeding strength was given until a positive reaction was obtained. Hereafter 1:10 first, first, 1:10 second and second strength PPD will be designated respectively as concentrations A, B, C and D.

All tests were done by the resident physicians and were read by them. A positive test was read if an area of induration of 5 mm. or more resulted.

Of the 338 admissions, 10 did not react to concentration D, and hence it was concluded that these patients did not have a tuberculous infection. One patient died before tuberculin could be given. Sixteen patients had insufficient data; either the tests were not completed or the usual series of dilutions was not used in testing. These were excluded. Two patients had proved carcinoma and were excluded, as was one patient with silico-tuberculosis. This left a total of 308 patients used in the report. These were classified either as (1) active pulmonary tuberculosis with positive sputum; (2) active pulmonary tuberculosis demonstrated by X-ray; (3) pleurisy with effusion present on admission or within six months prior to admission or (4) activity not demonstrated.

There were 32 patients admitted in whom no active tuberculosis could be proved by critical sputum studies or X-ray examination. However, each reacted to one of the four concentrations of tuberculin.

Of the 308 patients, there were 79 classified on admission as minimal, 138 as moderately advanced and 46 as far advanced, a total of 263 active cases.

Of the 308 patients, 20 gave a history of pleurisy with effusion. Their history varied from effusion present at the time of admission to fluid having been demonstrated twenty years previously. With these long histories of pleurisy with effusion, most patients lived a normal life with good health and no known activity. Several women in the group were delivered of one or more children.

Within one to several years after delivery they were admitted to the sanatorium with an active parenchymal lesion.

CASES IN WHICH ACTIVITY WAS NOT DEMONSTRATED

In 32 of the 308 patients, no active pulmonary tuberculosis could be demonstrated. Proof of negativity was accepted if at least one gastric washing was negative on culture and animal inoculation and if no X-ray changes indicative of active pulmonary tuberculosis could be demonstrated.

Of the 32 cases in which no activity could be proved, there were 12 patients (37 per cent)² who reacted to concentration A or B. In contrast, there were 20 patients (63 per cent) who failed to react to concentration A and B but did react to concentration C or D, almost a ratio of two to one in favor of the higher concentrations. Thus it would seem that inactive cases tend to have a lower degree of allergy.

ALL ACTIVE CASES

Of the 308 cases, 263 were demonstrated to have active pulmonary tuberculosis, either by the demonstration of tubercle bacilli or by X-ray evidence. Patients whose pleurisy with effusion occurred within six months prior to admission were not included in the 263. Of the 263 patients, there were 40 who reacted to concentration A. Of these 40, 25 (63 per cent) gave a history of one year or less (37 per cent longer than one year). One hundred twenty-five patients reacted to concentration B but failed to react to concentration A; of these 125 patients, 68 (54 per cent) gave a history of one year or less. Ninety-two patients reacted to concentration C but failed to react to concentrations A and B. Of these 92, only 34 (37 per cent) gave a history of one year or less. There were 6 patients who reacted to concentration D. One (18 per cent) gave a history of one year or less. It is apparent, therefore, that only a small percentage of the patients with a high degree of tuberculin allergy gave a long history of the disease.

There were 128 active cases with histories of one year or less, of which 93 (73 per cent) reacted to concentration A and/or B. There were 134 cases with histories longer than one year, of which 72 (53 per cent) reacted to concentration A and/or B.

It should be remembered that several of the patients who gave histories of five or more years had had long periods of intervening good health. Several of these long histories date from a period of pleurisy with effusion occurring as much as twenty years previously.

The average length of history in months in the 263 cases for the respective dilutions was:

Concentration A.....	31 months
Concentration B.....	33 months
Concentration C.....	52 months

²Fractions of percentages are omitted.

The median for these cases was:

Concentration A.....	8 months
Concentration B.....	11 months
Concentration C.....	23 months

This again seems to indicate that, on the average, those who were more sensitive had shorter histories than the less sensitive patients.

MINIMAL CASES

There were 79 minimal cases. Of the 8 cases reacting to concentration A, all gave a history of one year or less (100 per cent). There were 43 cases reacting to concentration B, 25 (53 per cent) giving a history of one year or less. There were 26 patients who reacted to concentration C but failed to react to concentration A or B. Only 11 (42 per cent) of these gave a history of one year or less. There were only 2 patients who failed to react to the three weaker dilutions, one with a history of eight months and one with a history of ten years.

Of the 79 minimal cases, 45 gave a history of one year or less. Of these 45 cases, 33 (77 per cent) reacted to concentration A or B, whereas 12 (23 per cent) reacted to concentration C or D.

There were 10 cases with histories longer than one year and up to two years. Six (60 per cent) reacted to concentration B. There were 12 cases with histories longer than two years and up to five years. Six (50 per cent) reacted to concentration B. There were 11 patients with histories of five years or longer, 6 (55 per cent) of whom reacted to concentration B.

The average duration of the history for the minimal cases was:

Concentration A.....	6 months
Concentration B.....	26 months
Concentrations C and D.....	34 months

The median was:

Concentration A.....	5 months
Concentration B.....	11 months
Concentrations C and D.....	23 months

MODERATELY ADVANCED CASES

There were 138 moderately advanced active cases, 23 of which reacted to concentration A. Twelve of these 23 (52 per cent) gave a history of one year or less. There were 63 patients who reacted to concentration B but failed to react to concentration A; of these 63, 36 (57 per cent) had a history of one year or less. There were 49 patients reacting to concentration C, failing to react to concentrations A and B, of whom only 17 (35 per cent) gave a history of one year or less. Thus, 65 per cent of those reacting to concentration C had a history of longer than one year. There were 3 cases reacting to concentration D, failing to react to the three weaker dilutions, one with a thirty-five-month history and 2 with ten-year histories.

Of the 138 moderately advanced patients 65 gave a history of one year or less, of whom 48 (74 per cent) reacted to concentration A or B. There were 73 cases with histories longer than one year; 38 (52 per cent) reacted to concentration A or B.

The average duration of history of these cases was:

Concentration A.....	43 months
Concentration B.....	37 months
Concentration C.....	49 months

The median was:

Concentration A.....	11 months
Concentration B.....	11 months
Concentration C.....	23 months

FAR ADVANCED CASES

There were 46 far advanced cases. Nine patients reacted to concentration A, 5 (56 per cent) of whom had a history of one year or less. There were 19 patients reacting to concentration B, failing to react to concentration A, of whom 7 (37 per cent) had a history of one year or less. There were 17 patients reacting to concentration C, failing to react to concentration A or B, of whom 6 (35 per cent) had a history of one year or less. Thus, 65 per cent of those reacting to concentration C had a history longer than one year. There was only one patient reacting to concentration D, failing to react to the three weaker dilutions, who gave a history of fourteen months.

Of the 46 far advanced patients 18 gave a history of one year or less, of whom 12 (67 per cent) reacted to concentration A or B. There were 28 with histories longer than one year, of whom 16 (57 per cent) reacted to concentration A or B.

The average duration of history for these cases was:

Concentration A.....	29 months
Concentration B.....	45.5 months
Concentration C.....	66 months

The median for these groups was:

Concentration A.....	5 months
Concentration B.....	35 months
Concentration C.....	47 months

PLEURISY WITH EFFUSION

There were 20 patients who gave a history of pleurisy with effusion. Seven cases had their symptoms six months or less previous to admission. Of these 7 cases, 5 (71 per cent) reacted to concentration C but failed to react to concentration A or B. Of those giving a history of one year or less, there were 10 (previous 7 included). Of these 10, 6 reacted to concentration C. There were 10 patients who had their pleurisy more than one year before admission, of whom 5 reacted to concentration D. Of these 10 patients, it should be noted that a

number enjoyed a period of several years of good health between the time of effusion and the present admission, which was motivated by a more recent parenchymal lesion.

STAGE OF DISEASE COMPARED WITH DURATION OF HISTORY

Of the 79 minimal cases, 57 per cent had a history of one year or less, with an average of thirty-eight months and a median of eleven months. Of the 138 moderately advanced cases, 47 per cent had a history of one year or less, with an average of thirty-six months and a median of seventeen months. Of the 46 far advanced cases, 39 per cent had a history of one year or less, with an average of fifty-one months and a median of twenty-three months.

STAGE OF DISEASE COMPARED WITH STRENGTH OF TUBERCULIN

Of all 79 minimal cases, 8 (10 per cent) reacted to concentration A, 43 (54 per cent) reacted to concentration B, 26 (33 per cent) reacted to concentration C and 2 reacted to concentration D. Of the 138 moderately advanced cases, 23 (16 per cent) reacted to concentration A, 63 (46 per cent) to concentration B, 49 (35 per cent) to concentration C and 3 (2 per cent) to concentration D. Of the 46 far advanced cases, 9 (19 per cent) reacted to concentration A, 19 (41 per cent) reacted to concentration B, 17 (38 per cent) reacted to concentration C and one reacted to concentration D.

It can be seen, therefore, that the total cases reacting to each concentration of tuberculin are divided among the minimal, moderately advanced and far advanced stages in about equal proportions.

COMMENT

It would seem from the above data that there is some correlation between the duration of history of tuberculosis and the tuberculin reactivity of the patient. We realize that our group is small and also that a history tends to be an inaccurate criterion for judging the duration of infection. Nevertheless, it does give a period during which the patient's reactivity may have a chance to vary. The far advanced cases, in particular, probably have the greatest error in the history, as 18 of the 46 cases (39 per cent) gave a history of one year or less and 11 (24 per cent) gave a history of six months or less. Probably most of these cases date their history much too recently.

There appears to be some significance in the fact that, in the minimal cases giving a history of one year or less, only 12 (23 per cent) failed to react to concentration A and/or B but reacted to concentration C or D, whereas 77 per cent reacted either to concentration A or B. In the moderately advanced cases with histories of one year or less, only 17 (26 per cent) and in the far advanced cases only 6 (33 per cent) failed to react to concentration A and/or B but reacted to concentration C.

The 8 minimal patients who reacted to concentration A had a history of one year or less. It should be noted that in all three stages the strength of tuberculin necessary to give a positive reaction increased as the duration of the history

increased. Apparently, the tuberculin sensitivity decreases as the period during which the patient had clinical evidence of tuberculous infection lengthens. It is suggestive that it is not the stage of the disease but rather the duration, which has this lessening influence on the allergy of tuberculous patients.

In those 32 patients in whom activity could not be demonstrated, 38 per cent reacted to concentration A and/or B. This small percentage is the reverse of that found in the patients in whom activity was demonstrated. In 128 active cases with a history of one year or less, 93 (72 per cent) reacted to concentration A and/or B. Thus, twice as many cases with a history of one year or less reacted to concentration A and/or B as did the inactive cases. Why this should be so, we cannot tell from our data. However, we do believe that it is shown that, in these patients, a high degree of allergy is less frequent than in those with active tuberculosis.

Of the 20 cases with pleurisy with effusion, it should be recalled that, of the 7 patients whose pleurisy began six months or less prior to admission, 5 (71 per cent) failed to react to concentration A or B but reacted to concentration C. This is in contrast to those patients with short histories and active parenchymal disease who were shown to have frequently a high degree of allergy.

In comparing the stage of disease (minimal, moderately advanced, far advanced) with the sensitivity of the patient, there appears to be no correlation, except in so far as the far advanced cases tend to have a longer history than the patients with moderately advanced or minimal lesions.

There is probably no practical value in such tuberculin testing from a prognostic or therapeutic point of view. However, from a diagnostic point of view it might be of aid, for, under the circumstances of X-ray evidence of a questionable lesion, a relatively short history and failure to demonstrate the presence of tubercle bacilli, a low degree of sensitivity would tend to indicate that the lesion is inactive. On the other hand, under the same set of circumstances, a high degree of sensitivity should make one hesitate to call the lesion inactive until an exhaustive search for tubercle bacilli has been made and a series of X-ray films has been obtained which proves the stability of the lesions.

CONCLUSIONS

1. There is no relationship between the stage of disease (minimal, moderately advanced, far advanced) and the degree of tuberculin sensitivity.
2. There is a tendency for the tuberculin sensitivity to be lower in patients with long histories and active pulmonary tuberculosis than in patients with short histories and active pulmonary tuberculosis.
3. The presence or recent presence of a pleurisy with effusion appears to lower the degree of tuberculin sensitivity.
4. Persons with an inactive tuberculous lesion tend to have a lower degree of tuberculin sensitivity than do those with active disease.
5. Tuberculin testing may, under certain circumstances, be an aid in evaluating a minimal lesion.

CONCLUSIONES

1. No existe relación alguna entre el período de la enfermedad (mínimo, moderadamente avanzado, muy avanzado) y la intensidad de la sensibilidad a la tuberculina.

2. En la tuberculosis pulmonar activa existe una tendencia a que la sensibilidad a la tuberculina sea menor en los enfermos con historias largas que en los enfermos con historias cortas.

3. La presencia actual o reciente de una pleuresía con derrame parece hacer bajar la sensibilidad a la tuberculina.

4. Las personas con una lesión tuberculosa inactiva suelen mostrar una sensibilidad más baja a la tuberculina que las que tienen la enfermedad en forma activa.

5. La comprobación con la tuberculina puede en ciertas circunstancias ayudar en el diagnóstico de una lesión mínima.

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STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS^{1,2}

Its Effect on Tuberculous Infections in Mice Produced by *M. Tuberculosis var. Hominis*

GUY P. YOUMANS AND JOHN C. McCARTER

Streptomycin, the antibiotic produced by *Actinomyces griseus*, has been shown to be markedly bacteriostatic *in vitro* for virulent human type tubercle bacilli (1, 2), and furthermore its activity *in vitro* is not affected, within wide limits, by the number of organisms nor by the presence of plasma (2). Feldman and Hinshaw (3) have also reported that this antibiotic exerts a suppressive action on tuberculous infections in guinea pigs.

Mice can be infected with virulent human type tubercle bacilli by either intraperitoneal or intravenous injection and when the latter route is employed the infection is principally pulmonary in type (4). Using mice infected intravenously with human type tubercle bacilli Gunn and Youmans (5) found that promin, diasone and promizole were ineffective in suppressing the infection, possibly because the toxicity of these compounds for mice is so great that therapeutic doses could not be tolerated. These compounds, however, are markedly effective in suppressing tuberculous infections in guinea pigs (6, 7, 8).

Experiment I: Thirty white Swiss mice, weighing approximately 25 g. each, were injected intravenously with 0.1 mg. of a twenty-one day old surface culture of the H37Rv human type strain of tubercle bacilli. The suspension of tubercle bacilli used for injection was prepared as previously described (9, 10). Twenty-four hours later 15 of the infected mice were given injections of 75 units of streptomycin hydrochloride³ dissolved in 0.2 ml. of sterile distilled water. These injections were repeated every six hours day and night for a period of twenty-eight days and were made under the skin of either the inguinal region, the abdomen or the back. The amount of streptomycin given to each mouse per day equaled 300 units and, on a relative weight basis, was equivalent to the dosage of streptomycin, 6,000 units per day, found by Feldman and Hinshaw (3) to be effective in suppressing experimental tuberculosis in guinea pigs.

At the end of twenty-eight days of continuous treatment 9 (60 per cent) of the 15 control animals were dead and 6 (40 per cent) of the streptomycin treated mice were dead. At this time the remaining surviving mice were sacrificed and examined. The complete viscera of each mouse were fixed in 4 per cent formaldehyde. Gross examination of the organs was followed by preparing sections of the lungs, liver, spleen and kidneys. Separate sections were stained

¹From the Department of Bacteriology and the Department of Pathology, Northwestern University Medical School, Chicago, Illinois, and the Evanston Hospital, Evanston, Illinois.

²This work was aided by a research grant from Parke, Davis & Company, Detroit, Michigan.

³Furnished through the courtesy of Dr. L. A. Sweet, Parke, Davis & Company, Detroit, Michigan.

TABLE 1

Time of death, weights and results of gross and microscopic examination of tissues of mice infected with 0.1 mg. H37Rv

MICE	TIME OF DEATH	WEIGHT AT DEATH	PER CENT OF LUNG SUBSTANCE OCCUPIED BY LESIONS	TUBERCLE BACILLI FOUND IN			
				Lungs	Liver	Spleen	Kidneys
Streptomycin Treated Mice†							
	<i>days</i>						
1	23	20	0	2+	1+	2+	1+
2	28*	19	25	3+	1+	1+	1+
3	28*	23	10	2+	1+	1+	1+
4	28*	22	50	4+	1+	3+	3+
5	28*	23	0	3+	1+	2+	0
6	9	23	20	1+	1+	1+	1+
7	15	20	5	3+	1+	1+	1+
8	28*	19	10	4+	2+	1+	1+
9	28*	16	30	4+	2+	2+	1+
10	28*	23	50	2+	1+	1+	1+
11	12	25	0	2+	0	0	0
12	24	11	30	3+	0	1+	1+
13	28*	27	0	1+	1+	1+	0
14	28*	17	10	1+	1+	1+	1+
15	28*	20	50	3+	1+	1+	2+
Average....	24.2	20.5	19.3	2.5	1.0	1.3	1.0
Control Mice							
1	18	15	75	4+	1+	1+	1+
2	24	17	40	4+	2+	2+	2+
3	24	11	60	4+	1+	1+	2+
4	28*	18	0	1+	1+	1+	1+
5	28*	14	10	1+	1+	1+	1+
6	18	17	50	4+	2+	3+	2+
7	20	13	70	4+	1+	1+	1+
8	24	10	60	4+	1+	2+	1+
9	28	11	50	4+	1+	1+	1+
10	28*	22	30	2+	1+	1+	1+
11	20	12	50	4+	3+	3+	1+
12	23	11	50	4+	3+	2+	1+
13	28*	22	10	1+	1+	1+	1+
14	28*	15	50	4+	2+	2+	1+
15	28*	20	10	2+	1+	1+	2+
Average....	24.4	15.2	41.0	3.1	1.5	1.5	1.3

* = killed at termination of experiment.

† = 300 units of streptomycin per day.

1+ = one to several bacilli per section.

2+ = single bacilli and small clumps of bacilli.

3+ = large clumps of bacilli.

4+ = very large and numerous clumps of bacilli.

with hematoxylin and eosin, and with Ziehl-Neelsen carbol fuchsin, respectively. An estimation of the percentage of lung substance occupied by "tubercles" was made both grossly and microscopically and in the Ziehl-Neelsen stained sections an estimate of the numbers of tubercle bacilli found in the various organs was made. These results were tabulated in table 1.

The 15 untreated control mice in this experiment, upon gross examination, showed extensive involvement of the lungs with "tubercles" which averaged 41 per cent of the total lung substance. The lungs were also enlarged and generally heavily congested. No gross lesions were seen in any other organs.

Microscopically the lungs of this set of mice showed small, large and conglomerate "tubercles." These lesions were characterized by a variable amount of coagulative necrosis of the lung framework and by exudate, surrounded by a dense infiltration of monocytes, a few lymphocytes and an occasional polymorphonuclear leucocyte. A few of the phagocytes had a foamy cytoplasm. No foreign body giant cells nor epithelioid cells were seen, the lymphocytic infiltration was slight, and there was no indication of fibrosis. Thus the lesions lacked the typical architecture of human tubercles. In addition no lesions were found comparable to tuberculous pneumonia in the human. Acid-fast bacilli were found in these lungs in large numbers lying in clumps in the necrotic tissue; many of the phagocytes contained one or more organisms.

The spleens of these animals showed a diffuse and irregular proliferation of the reticuloendothelial cells in the pulp and corpuscles with occasional tiny areas of necrosis. Tubercle bacilli were present singly and in small clumps in the necrotic areas but more commonly in the phagocytes.

In the livers were found scattered small infiltrations of monocytes without regard to lobular anatomy. Occasionally a tiny area of necrosis was seen. There was no typical tubercle formation and only an occasional lymphocyte was seen. Acid-fast organisms were found singly and in small clumps in these infiltrations; a few sinusoidal endothelial cells contained one or two bacilli.

The kidneys showed small aggregations of mononuclear cells arranged perivascularly in the cortex and in some glomeruli, but only infrequently in the medulla. In 2 animals there were microscopic areas of coagulative necrosis. Without exception tubercle bacilli singly and in small clumps were found in these lesions.

The extent of the lesions in the lungs, together with the large numbers of bacilli, is to be expected from the intravenous route of infection. The invariable finding of small numbers of bacilli in the inconspicuous lesions of the liver, spleen and kidneys may possibly represent the result of secondary blood-stream dissemination.

The lesions in the 15 streptomycin treated mice were qualitatively similar to those found in the controls. However, 4 of these mice showed no evidence of gross lesions in the lungs and only 3 had as much as 50 per cent involvement of the lung substance. The overall average amount of lung substance involved in these animals was only 19 per cent (table 1).

Table 1 also gives the survival times of the animals of both groups and the

TABLE 2

Time of death, weights and results of gross and microscopic examination of tissues of mice infected with 0.1 mg. H37Rv

MICE	TIME OF DEATH	WEIGHT AT DEATH	PER CENT OF LUNG SUBSTANCE OCCUPIED BY LESIONS	TUBERCLE BACILLI FOUND IN			
				Lungs	Liver	Spleen	Kidneys
Streptomycin Treated Mice†							
	days						
1	10	25	0	1+	1+	1+	0
2	28*	25	0	1+	1+	1+	1+
3	28*	24	0	1+	1+	1+	1+
4	28*	28	0	1+	1+	1+	1+
5	28*	25	0	1+	1+	1+	1+
6	3	25	0	1+	1+	1+	0
7	28*	22	0	1+	1+	1+	1+
8	28*	30	0	1+	1+	1+	1+
9	28*	28	0	1+	1+	1+	1+
10	28*	25	0	1+	1+	1+	1+
11	28*	25	0	2+	1+	1+	1+
12	28*	23	0	1+	1+	1+	1+
13	28*	30	0	1+	1+	1+	1+
14	28	28	0	1+	1+	1+	1+
15	28*	25	0	1+	1+	1+	1+
Average....	25.1	25.8	0	1.06	1	1	0.86
Control Mice							
1	18	19	40	3+	1+	1+	0
2	21	18	50	2+	1+	0	0
3	23	12	25	4+	3+	3+	4+
4	27	17	40	3+	2+	1+	2+
5	17	19	30	3+	1+	1+	1+
6	18	20	50	3+	1+	1+	1+
7	18	20	25	2+	1+	1+	1+
8	28*	25	10	2+	1+	1+	1+
9	18	20	40	3+	1+	1+	1+
10	19	16	50	3+	1+	1+	1+
11	20	20	60	4+	1+	1+	1+
12	18	17	60	4+	2+	2+	1+
13	21	20	40	3+	3+	1+	1+
14	27	15	50	3+	1+	1+	2+
15	28*	25	10	2+	2+	1+	2+
Average....	21.4	18.8	38.6	3	1.5	1.1	1.3

* = killed at termination of experiment.

† = 3,000 units of streptomycin per day.

weights at death or when sacrificed. Both groups lost weight progressively over the course of the experiment but this was more marked in the controls than

in the treated animals. There was no significant difference in the average survival times.

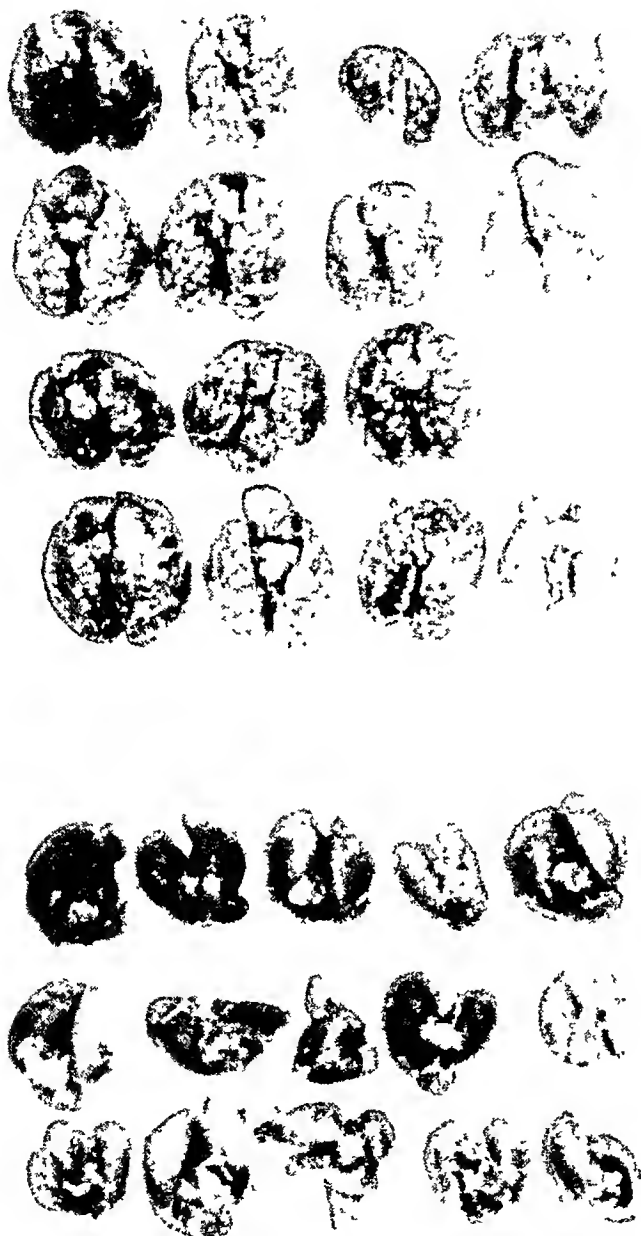


FIG. 1. (Upper) Lungs of control mice, Experiment II. Natural size.

FIG. 2. (Lower) Lungs of streptomycin treated mice, Experiment II. Natural size.

Experiment II: The results of the previous experiment did not show any significant difference between the streptomycin treated animals and the untreated



FIG. 3. (Upper) Typical microscopic section of lung of control mouse, Experiment II.
× 120

FIG. 4. (Lower) Typical microscopic section of lung of streptomycin treated mouse,
Experiment II. × 120

controls. The slight differences observed, however, in mortality, extent of lesions and weights between the two groups were suggestive enough to warrant the use of much larger doses.

In this second experiment the same procedures were followed as before except

that the total daily dose of streptomycin was raised to 3,000 units and treatment was started on the day the mice were infected.

When the experiment was terminated twenty-eight days after the mice were infected, 13 (87 per cent) of the streptomycin treated animals were living whereas only 2 (13 per cent) of the controls were still alive. The 2 treated mice died early, three and ten days, respectively, after the beginning of the experiment, whereas the first control animal died seventeen days after. The difference in the appearance of the animals in the two groups over the course of the experiment was striking. The control animals progressively lost weight and became emaciated, whereas the streptomycin treated mice not only maintained their weight but most of them gained slightly. The average weight loss in the controls was 27 per cent (table 2).

The striking difference in mortality and appearance between the two groups was paralleled by the gross and microscopic appearance of the viscera, especially the lungs. The 15 controls showed lesions qualitatively and quantitatively similar to those of the controls in the first experiment. The lungs of all exhibited gross lesions (figure 1) the average estimated lung substance occupied thereby being 39 per cent. Tubercle bacilli were found in the lungs of all these mice in large numbers. Organisms were also found in the other organs (table 2) (figure 3).

In the streptomycin treated group of animals, on the other hand, no gross lesions were present in any of the mice (figure 2). The microscopic lung lesions consisted only of small scattered infiltrations of peribronchial tissues and alveoli with mononuclear phagocytes, many of which had a foamy cytoplasm (figure 4). Only one animal showed microscopic areas of necrosis. Acid-fast bacilli were, however, present in all mice, but in markedly fewer numbers as compared with the controls. Microscopic lesions were also found in the liver, spleen and kidneys but were smaller and more sparsely distributed than in the controls. These organs contained acid-fast bacilli but the organisms occurred almost always only singly in the phagocytes; frequently a complete search of a section of one of these organs revealed only one or two organisms. It was also noted that many more of the phagocytes in these animals had a foamy cytoplasm possibly indicating more digestion of ingested tubercle bacilli.

In the 60 mice used in the two experiments only 2 animals showed adventitious lesions, one an infarct of the spleen and one an encapsulated nidus of unidentified parasites in the liver. No essential difference in the condition of the organs examined, other than the quantitative difference in tuberculous lesions, was noted between the untreated and treated sets of animals, indicating that the streptomycin was nontoxic in the doses used.

DISCUSSION

The results reported in this paper clearly show that streptomycin exerts a marked suppressive effect on experimental pulmonary tuberculosis of the mouse. That the infection is not completely suppressed is shown by the presence of microscopic lesions containing tubercle bacilli. However, the infecting dose of

tubercle bacilli was large and the period of treatment relatively short. Furthermore, since streptomycin is rapidly excreted from the body it is possible that, with the limited number of daily injections used, contact between the antibiotic and the tubercle bacilli in the tissues occurred for only a portion of each twenty-four-hour period. Smaller amounts of streptomycin, especially if given more frequently, might be equally effective.

In terms of units the amount of streptomycin used in the successful experiment was large, 120,000 units per kilo, but was apparently well within toxic limits since no deleterious effects were noted.

These results with streptomycin further indicate that mice may be suitable animals to use when testing chemotherapeutic agents *in vivo* against human type tubercle bacilli. The practical advantages would be that the results could be obtained in a shorter time, a larger number of substances could be tested at one time because of the smaller amount of cage space necessary, and the amount of each test substance needed would be markedly reduced. From the theoretical standpoint, since mice are far more resistant animals than guinea pigs and because the infection is primarily pulmonary in type, the results might be more analogous to those that would be obtained in treating tuberculosis in the human. Further work will be needed to test the validity of the latter possibilities.

SUMMARY

Streptomycin hydrochloride administered subcutaneously had a marked suppressive effect on experimental pulmonary tuberculosis in mice. The use of mice for testing the effect of chemotherapeutic agents on experimental tuberculosis is discussed.

SUMARIO

El clorhidrato de estreptomicina administrado subcutáneamente ejerció un decidido efecto cohibidor sobre la tuberculosis pulmonar experimental del ratón. Discútese también el empleo de los ratones para comprobar el efecto de las sustancias quimioterapéuticas sobre la tuberculosis experimental.

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AMERICAN TRUDEAU SOCIETY

Report of the Committee on Postgraduate Medical Education

Dr. Paul P. McCain, *Chairman*

Dr. J. Burns Amberson

Dr. Chesley Bush

Dr. Charles A. Doan

Dr. Esmond R. Long

Dr. James J. Waring

The Committee on Postgraduate Medical Education has had only one meeting. This was held at the Cosmos Club in Washington, D. C., on October 31, 1944. Colonel Esmond R. Long, Drs. J. Burns Amberson, James J. Waring, Cameron St. C. Guild, Paul McCain and, by invitation, Drs. Bruce Douglas, Herbert R. Edwards and Captain William H. Roper were present.

It was felt that the most important function of our Committee would be to assist physicians returning from the armed services who would wish postgraduate training in tuberculosis and diseases of the chest to secure positions in accredited sanatoria and hospitals. It was felt that emphasis should be placed on the importance of training in pulmonary diseases not only for those who expected to specialize in tuberculosis but also for all those planning to practice internal medicine. Our Committee expressed the wish to coöperate with other organized medical groups working to the same end. Dr. Cameron St. C. Guild, our Executive Secretary, was authorized to confer with representatives of the American College of Physicians, the American College of Surgeons and the American Medical Association and offer to these groups the full coöperation of our Association.

It was found that the American Medical Association had sent questionnaires to 21,000 physicians in the armed services to find out what postwar training they desired. They had also sent questionnaires to all hospitals and sanatoria accredited for residencies and fellowships to learn what openings there would be available for returned physicians from the armed services. We were surprised and somewhat disappointed to learn that relatively few of the physicians now in the armed services expressed a desire to get special training in tuberculosis and diseases of the chest on their return to civil life. It is evident that there will be a sufficient number of positions available in accredited sanatoria for all who desire training in pulmonary diseases.

While attending another committee meeting in Chicago, Drs. Guild and McCain had conferences with General Charles R. Reynolds, Executive Secretary of the American College of Surgeons, and with Dr. Victor Johnson, Executive Secretary of the Council on Medical Education of the A. M. A., both of whom assured us that their organizations would be glad to coöperate with our Committee in every possible way.

At the meeting of our Committee in Washington it was the consensus that our various Trudeau sections can perform a worth while function in postgraduate medical education and especially so if at their meetings they can have a promi-

nent, possibly an out-of-state, speaker who will attract the members of the medical profession at large. Since dues in these sections are nominal, it was thought that the American Trudeau Society, the parent organization, should be prepared on request to finance a prominent out-of-state speaker on tuberculosis for annual meetings of our sections.

Sponsorship of the International Medical Congress at Laredo and possibly later of the postgraduate medical meetings for Negro physicians by our Committee was approved in case such a change should be approved by the Council. In case such a change is made, a budget item will need to be provided for the expense of these meetings heretofore carried by the Committee on Tuberculosis among Spanish People and the Committee on Negro Program.

The matter of medical books available to the NTA members was discussed. Since the list as published by the NTA has in the past been subjected to some minor criticism, members of the Committee felt that the list should be reviewed, and the Committee agreed to do so if requested by the National Tuberculosis Association. This would tend to prevent the inclusion of somewhat inferior books and the possible omission of some more worth while.

A discussion was also had concerning the Abstracts. The Committee expressed its willingness to review the Abstracts for the past year, bearing in mind primarily whether or not the subject matter covered that in which the general practitioner would be interested. Any recommendations or suggestions made by the Committee would be passed on to Doctor Lyght for his consideration.

Hearty approval was given to the suggestion made by Doctor Waring that the Committee recommend that consideration be given to the production each year of a series of brief articles on the progress in the field of tuberculosis control, or recent advances in the field of chest radiology, thoracic surgery, chemotherapy, laboratory diagnosis and clinical phases. Should the Council approve of this recommendation, it is felt that the Chairmen of the appropriate Trudeau Committees might be requested to arrange for such a résumé covering their particular field. It is the opinion of the Committee that these résumés might be widely used by medical journals throughout the country.

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Evaluation of Laboratory Procedures

Dr. C. Eugene Woodruff, *Chairman*

Dr. Harry J. Corper

Dr. Max Pinner

Dr. David Crombie

Dr. David T. Smith

Dr. Edgar M. Medlar

*Mr. William L. Steenken

The Committee on Evaluation of Laboratory Procedures had a profitable meeting in Chicago, February 2, 1945. In attendance were Dr. C. Eugene Woodruff, Chairman, Dr. Harry J. Corper, Dr. Edgar M. Medlar, and William L. Steenken, N. T. A. member.

Discussion centered on the following subjects:

1. A statistical study of leucocyte counts which, at Doctor Pinner's suggestion, has been prepared by Mr. W. N. Berg. This paper, showing the very considerable error which may be expected in the average leucocyte count, is to be published in the *Review* (September, 1945).
2. The drawing up of a formula for a standard medium for the culture of tubercle bacilli. Members of the Committee are, at the present time, trying variations of the proposed standard medium in the attempt to discover the one which will produce optimum growth of the tubercle bacillus.
3. A brief report on the use of detergents in treating sputum and other material, to be prepared by Mr. Steenken.
4. An apparatus suggested by Doctor Medlar to be used in micro-determination of red cell sedimentation rates.
5. Microscopic examination of tubercle bacillus cultures negative for growth by gross examination.

As indicated above, the subject of a standard medium for culturing tubercle bacilli is being pursued actively at the present time. Dr. C. E. Palmer of the Tuberculosis Control Division, U. S. P. H. S., has indicated his interest in this subject and his desire to collaborate in every way possible.

The matter of defining a "negative sputum" was discussed in a joint session with the Committee on Therapy. The members of the Laboratory Committee stand ready to give their opinion either individually or collectively regarding any proposed change in the definition of "negative sputum."

*National Tuberculosis Association Member.

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Medical Program

Dr. H. S. Willis, *Chairman*

Dr. Howard W. Bosworth

Dr. Max Pinner

Dr. H. Corwin Hinshaw

Dr. James C. Walsh

The Committee on Medical Program for 1945 can make an exceedingly brief report because of the obvious fact that the annual meeting was cancelled shortly after the Committee began its work. A tentative and preliminary outline was set up at the meeting of the Committee in such a way as to stress:

Committee reports

Noninfectious pulmonary disease

A review of the present status of trends in thoracic surgery

A symposium on rehabilitation under the title "Medical Management of the Recovery Phases of Tuberculosis"

Diagnostic roentgenology

Mass radiography

Nutritional deficiency diseases and (by way of joint session with the Public Health Section)

A national program for tuberculosis control in which the new efforts of the U. S. Public Health Service and its relationships to state health officers, state tuberculosis associations and private physicians would be elaborated.

This was the status when cancellation of the meeting occurred.

AMERICAN TRUDEAU SOCIETY

Report of the California Trudeau Society

Dr. C. Gerald Scarborough, *Secretary*

The following is a summary of the activities in which the California Trudeau Society has engaged during the past year.

Arrangements have been made so that any private physician outside of metropolitan areas can send a chest X-ray film to the association office and a competent member of the Trudeau Society will supply an interpretation and return the film to the physician together with comments on technique.

Members of the California Trudeau Society have traveled to a number of the rural counties in the state for teaching clinics. These clinics were arranged so that the private physicians brought their patients in for examination and consultation. Only 10 per cent of the total number of patients handled were allowed to come from the health department, so that it was predominantly a private patient group examined.

Postgraduate courses ranging from two to ten days were given to six physicians in the state. The work included time at the University of California Medical School, Stanford Medical School and at the Highland-Alameda County Hospital at Oakland.

In view of the recent restriction of the O. D. T., we are holding our annual meeting in a streamlined form, one in Los Angeles for the benefit of the members in the southern part of the state, and one in San Francisco for members in the northern part. Dr. Herman Hilleboe will be the guest speaker at both of these meetings and will present plans of the Tuberculosis Control Division of the U. S. Public Health Service. There will be a presentation of the problems of returning veterans and of problems in miniature X-ray techniques and surveys.

We are contemplating putting out a directory of the members of the California Trudeau Society similar to that put out by the American Trudeau Society.

Eighteen new members have been added to the roster of the Society this year, and there are 49 members in the armed forces.

AMERICAN TRUDEAU SOCIETY

Report of the Minnesota Trudeau Medical Society

Dr. S. T. Sandell, *Secretary-Treasurer*

A meeting of the Minnesota Trudeau Medical Society was held in St. Paul on November 3, 1944. Forty-five members were present at the meeting, at which Dr. S. S. Cohen, Chairman of the Executive Committee, announced that he appointed a Sanatorium Consultation Committee as follows: Drs. G. A. Hedberg, Thomas J. Kinsella, L. M. Larson, A. M. Olson, Karl H. Pfuetze, Thomas Lawry and E. P. K. Fenger, Chairman.

The following activities have been sponsored by the Committee:

The Committee held a meeting with the Michigan and Wisconsin Committees at Pembine, Wisconsin, on June 3 and 4, 1944. Doctor Fenger presented 75 cases for Glen Lake Sanatorium for review and discussion by the three combined Committees. At the second meeting of the Sanatorium Consultation Committee, held on September 30th and October 1st, the cases from Mineral Springs Sanatorium were presented by Doctor Pfuetze. On January 26, 27 and 28, 1945, the Committee visited Nopeming Sanatorium, where all the cases in residence were reviewed. Both the Committee and the Nopeming Sanatorium staff felt that the meeting was very worth while. Another combined meeting of the Minnesota, Wisconsin, and Michigan Sanatorium Advisory Committees is scheduled at Pembine, Wisconsin, on June 15th and 16th. Dr. G. A. Hedberg will present 75 successive first admission cases from Nopeming Sanatorium.

At the fall meeting, considerable discussion took place regarding what constituted a reportable case of tuberculosis. It was decided that all cases of tuberculosis, both pulmonary and extrapulmonary, active and inactive, should be reported to the State Board of Health. The Society passed a resolution requesting the legislature to provide 25 beds in one of the state institutions for incorrigible patients who refused to obey sanatorium rules or who refused to remain in a sanatorium until such time as they were no longer a public health menace. Dr. E. S. Mariette, the Chairman of the Legislative Committee, suggested that the Society recommend certain legislation pertaining to the rehabilitation of the tuberculous and committing positive-sputum cases to the public sanatoria. The Society voted approval of the legislation. Some of these bills have already become law. A paper on *The St. Louis County Tuberculosis Survey* was presented by Dr. Roberts Davies, Nopeming, and one on *Tuberculous Bronchiectasis* by Dr. S. S. Cohen, Oak Terrace.

Another meeting of the Society was held in Minneapolis on March 2, 1945 at which 52 members were present. The following papers were presented: *The Laboratory Diagnosis of Tuberculosis* by Dr. Wm. H. Feldman, Rochester, and *What Categories of Patients Should Be Considered as Having Positive Sputum* by Dr. H. Corwin Hinshaw, Rochester and Dr. F. F. Callahan, Ah-gwah-ching. A committee, of which Doctor Callahan was chairman, attempted to answer the last question by a committee report which follows.

Another meeting of the Minnesota Trudeau Medical Society is scheduled for late May or early June. The speakers have not as yet been selected.

Report of Special Committee

Dr. F. F. Callahan, *Chairman*

Dr. Roberts Davies

Dr. F. M. Feldman

Dr. Frank Hill

Dr. E. S. Mariette

The following Committee report was submitted to the Minnesota Trudeau Medical Society at its meeting in Minneapolis on March 2, 1945.

In controlling the spread of tuberculosis, the greatest problems are presented by the unknown cases, the terminal cases cared for in the home, and the completely uncoöperative cases with positive sputum. It is hoped that the group surveys now planned will bring the majority of the unknown cases to light. All terminal cases should be isolated in sanatoria whenever and wherever possible. All cases with positive sputa, even if the bacilli are found only on culture of sputum or gastric contents, should be isolated if they refuse medical observation.

The group of patients who have had sanatorium care and training and who are apparently clinically inactive but who show some degree of pathological activity, as indicated by the occasional presence of tubercle bacilli in the sputum or gastric contents, deserve special study and consideration. Their continued isolation (in the sanatorium) or discharge should be determined by the staff of the sanatorium where these patients were treated, in collaboration with the local and state health departments. In reaching a decision, consideration should be given to the following: the type, age and extent of the pulmonary lesion; the sex, age and resistance of the patient; his intelligence and economic status; his economic usefulness; his family and civic responsibilities; and finally the type of work for which he has been trained.

In making these recommendations, it is assumed by the Committee that all patients in the questionable group will have medical follow-up examinations at three-month intervals for the first year and at six-month intervals thereafter. We believe this should be the minimum requirement in the follow-up of this group of patients.

It is the opinion of the Committee that the patient who has had adequate treatment and training is less of a public health hazard than the untrained or untreated patient.

AMERICAN TRUDEAU SOCIETY

Report of the Illinois Trudeau Society

Dr. L. L. Collins, *Secretary-Treasurer*

The Illinois Trudeau Society held a meeting in Chicago on April 5, 1945, in conjunction with the Chicago Tuberculosis Society and the Illinois Chapter of Chest Physicians. The meeting was called to order by the president of the Chicago Tuberculosis Society with short greetings extended by the presidents of the other two collaborating societies.

Captain David J. Dugan, M. C., gave an interesting and enlightening talk on the manner of handling chest injuries which was accompanied by colored motion pictures of actual operations. Dr. Henry C. Sweany gave an excellent negative report on the therapeutic results with sulphone compounds. He left little doubt in the minds of those present that, as yet, no adequate chemical compound has been found which will successfully combat tuberculosis. Doctor Sweany pointed out, however, that such negative reports should not discourage research work, but should offer stimulation toward greater effort.

There were between 75 and 100 people present at the meeting, of whom approximately 60 per cent were members of the Illinois Trudeau Society; practically all of them were members of the Chicago Tuberculosis Society, and most were members of all three societies.

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Artificial Respiration.—Seven different forms of mechanical artificial respiration were studied in animal experiments for their influence on the pulmonary and systemic blood pressure. The trachea of the animal was cannulated to insure a free airway. Balloons were inserted into the thoracic and abdominal cavities in order to record changes in the pressure relationship. The gross and net pressures in the pulmonary and coronary arteries were measured by special arrangements in the not operated on and unanesthetized animal. Sounds were inserted into the right and left ventricles. Various degrees of reduced cardiac activity with severe depression or complete arrest of respiration were produced by various methods. Recovery of the animal was accomplished when respiratory arrest and slow weak cardiac contractions were produced with helium regardless of the method of mechanical respiration employed. Only insignificant changes in pulmonary and systemic blood pressure were observed when cardiac and respiratory arrest occurred, either by helium or by electrically induced ventricular fibrillation. The blood flow produced by the resuscitator did not reach the coronary and cerebral arteries. The so-called "milking action" of the intrapulmonic positive-negative type of resuscitator did not effectively increase the return of blood to the heart.—*Influence of Different Forms of Mechanical Artificial Respiration on the Pulmonary and Systemic Blood Pressure, P. P. Volpitta, R. A. Woodbury & B. E. Abreu, J. A. M. A., December 23, 1944, 126: 1066.*—(H. Abeles)

Mass Surveys.—The material consisted mostly of selective service registrants between

18 and 35 years of age. The majority were from the South and, of these southerners, 47.1 per cent were colored. There were 223,182 stereoscopic 4 x 5 films taken; 14 x 17 X-ray films were taken of all suspicious cases. The incidence of disabling chest diseases, both of a permanent and temporary nature, was 1.018 per cent. Active tuberculosis was found in 0.3284 per cent. It is emphasized that known cases of active tuberculosis are placed in 4-F by local draft boards and not sent to the induction stations for examination. Prognoses were attempted on the following basis: minimal involvement in one or both lungs was considered to have a good prognosis, moderately advanced or far advanced disease confined to one lung was also considered to have a good prognosis, moderately advanced or far advanced disease in one lung associated with either minimal or moderately advanced disease in the contralateral lung was considered to have a fair prognosis, and bilateral far advanced disease was considered to have a poor prognosis. On this basis, 77.4 per cent were considered to have a good prognosis, 3.8 per cent a fair prognosis, and 17.9 per cent a poor prognosis. All chest rejectees from Mississippi were sent to the State Sanatorium for observation and follow-up by county health authorities. One group included in the study consisted of soldiers to be discharged for dependency or over-age. Of these, 0.8 per cent were found to have a disabling chest disease. None had had symptoms sufficient to have warranted investigation by their regimental medical officers. Routine chest X-rays films were not being made when these soldiers entered the Army. In a group whose physical examinations were

complete before the X-ray films were read, only 12.7 per cent of those with rejectable chest disease had shown significant physical signs. Only 14 out of every 100 cases of active tuberculosis would have been suspected from physical examination alone. No account was made of the incidence of minor calcified deposits, but a check on 5,000 plates chosen at random with this in mind revealed an incidence of 38 per cent. Only the films with marked calcification were noted; 0.016 per cent had dextrocardia. One out of every 140 had some congenital rib anomaly. This is an incidence of 0.7133 per cent. There were 452 cases of cervical ribs. There was no relation between the presence of rib defects and the incidence of disqualifying lung diseases. One hundred and fifty-nine cases of disqualifying severe pleural involvement were found; 31 of these had calcified deposits in the pleura. There were 6 diaphragmatic herniae, all proved by barium meal. Five were on the left side. There were 28 cases of pneumothorax simplex without apparent cause. The author pointed out that the majority of the cases of active tuberculosis were found early and treatable, demonstrating the excellence and practicability of mass X-ray technique in case-finding.—*The Chest X-ray, Major D. G. Morse, F.C.C.P., Dis. of Chest, November-December, 1944, 10: 515.*—(K. R. Boucot)

Photofluorography for Chest Surveys.—The problem of the detection and control of tuberculosis is of paramount importance to the government and the civilian. An important factor in the control of tuberculosis is the finding of the unsuspected case and the placing of such cases under proper supervision. Of prime concern are the minimal cases who are asymptomatic and unknowingly jeopardize themselves and those with whom they come in contact. Formerly surveys were impractical because of the expense. However, photofluorography is not only a relatively inexpensive method, but is practical, adequate and reliable. While others have written in this vein, the author writes

to further confirm this impression, and, therefore, has reviewed his work, as roentgenologist at the Great Lakes Naval Training Station. Of the four methods of conducting surveys, that is, the use of standard 14 x 17 inch films, the use of 14 x 17 inch paper, photofluorography using 4 x 5 inch films with stereoscopic views and photofluorography using 35 mm. films, the author believes that the photofluorographic method using the 4 x 5 inch film is the most adequate. In its favor is the low cost, the rapidity per case, simplified filing and the reliability of the film for interpretation. He feels that the percentage of error should be as low as that with the large film. These films can be read without magnification and without undue eye strain. The 35 mm. film was the type used at the Great Lakes Station. The X-ray machine was a standard two hundred milliamperere one with a movable tube stand. The photofluorographic unit was equipped with a large Leica with a film capacity of thirty feet and having a 1-5 lens. The screen distance was thirty-six inches and the tube-film distance forty inches. The tube and camera were fixed in place, the patient being raised or lowered in front of the screen by means of an electric elevator. One hundred foot rolls of film were cut into thirty-three foot lengths, each filling of the camera caring for two hundred exposures. The time consumed in processing the film, using standard solutions, was about one hour. Usually an average of 240 cases an hour was maintained, though on a few occasions as many as 420 per hour were cared for. However, the 240 per hour was more economical as far as wear and-tear on the tube is concerned, the average life of a tube being 5,700 exposures. The speed of interpretation with brief reports was about 400 per hour. If anything of a suspicious or pathological nature was noted in the microfilm, the man was rechecked with a 14 x 17 inch film. If the findings were important, the patient was referred to the Naval Hospital for disposition. At the hospital he was given a thorough examination and the case referred to the Medical Examiners Board for

final decision. When active tuberculosis was found, the patient was sent home, the Board of Health in his home town notified of the facts by the Red Cross, and they in turn saw that he had proper care. A careful record of all such cases was kept. There were 400,263 cases X-rayed. These represented a good cross-section of the male population of the country including men from all walks of life. Their ages ranged from 17 to 45 with the majority between 17 and 35. The accuracy of the films was checked as films and reports were returned from the hospital at the end of each month with data concerning the correct diagnosis and disposition of the patient. Taking two representative months, the total films rechecked with a 14 x 17 film was 317, 112 of which were sent to the hospital for disposition and confirmation. The number confirmed was 96 (35.7 per cent), the number of diagnosis changed was 16 (14.28 per cent). These included 7 active tuberculosis changed to inactive, 3 pneumonitis changed to atypical pneumonia, 2 tuberculosis changed to atypical pneumonia and 4 inactive primary tuberculosis of possible significance to no significance. These errors in judgment were somewhat excusable as the diagnoses were made from the X-ray films alone with no history or clinical data. Consequently, most diagnoses were made as pessimistic as possible. Since the beginning of the survey, 6 patients with negative diagnoses have been hospitalized with active tuberculosis. There are two possibilities as to why these were missed, first, the size of the lesion and the smallness of the X-ray film, or, second, the first diagnosis was correct and the condition developed after entry into the service. There is no doubt that this survey was of value, for 897 of the 400,263 men examined were discharged from the service with tuberculosis. All have been placed under proper treatment which is of importance to the patient and his contacts. For each case it was estimated that it has saved the government twenty-five thousand dollars. Even though the 35 mm. film does not approach the accuracy of the larger 14 x 17 inch film, it is ade-

quate enough for practical purposes. It is conceivable that some day a system may be devised whereby the entire population of a community may be surveyed with the result that active cases can be isolated and so supervised as to make the incidence of tuberculosis insignificant. — *Photofluorography for Chest Surveys*, M. W. Mason, *Radiology*, November, 1944, 43: 499.—(G. F. Mitchell)

Tuberculosis in Armed Forces—In World War I many thousands of tuberculous soldiers were inducted into service because of inadequacy of methods of detecting the disease. X-ray examination was not always done when mobilization began in 1940. Not until 1942, and only after approximately one million men had been admitted without X-ray examination, did this procedure become universal. The objective of physical standards in both the Army and the Navy was to exclude all active tuberculosis and all inactive disease that might be reactivated under strain of military duty. These criteria are briefly reviewed and note is made of the fact that at first these standards were quite rigid, especially in relation to calcified primary lesions. These were later liberalized. These varying standards affected the rejection rates at different periods. Thus early in 1942 the rejection rate was about 16 per 1,000. In the latter part of 1942 it dropped to about 10 with the liberalization of the standards for admission. The rate of rejectees was higher among white than among colored recruits and, in 1943, it was higher for women than for men. At first not all cases rejected for tuberculosis were reported to the state health boards. Later this was made compulsory. Films of accepted men at the time of induction are filed at the Veterans Bureau. Every soldier is X-rayed before discharge. Comparison can thus be made between the initial and final status of every man in the armed forces. During the course of the present conflict the admission rate for tuberculosis has been approximately one-tenth of that of World War I. This decrease reflects the lower incidence of tuberculosis in the general popu-

lation but especially the greater efficiency of modern procedures in excluding cases at the time of induction. The highest rate was 3 per thousand in 1941 and represents a large number who had been inducted during the early phase of mobilization without adequate X-ray control. The admission rate for tuberculosis overseas is lower than for troops in continental United States as the former represent a more selected group. A comparison of the X-ray films of men at the time of their breakdown with tuberculosis with their induction films reveals, in the majority of instances, that the disease had already been present at the time of induction but was missed. The rate of discharge for tuberculosis from the Army has varied from 2 to 0.5 per thousand. Early in 1942 it was high, later with changes in policy in relation to retention of cases of inactive tuberculosis for limited service this rate fell to the lower figure noted above with approximately 3,500 discharges per year in an army of 7,000,000 soldiers. It is noteworthy that the discharge rate for tuberculosis increases with the age of the individuals. Thus, while only 0.30 per thousand under 20 are discharged, 1.32 of 35 to 39 years are discharged for tuberculosis. All army and naval personnel are X-rayed before release from active duty. While the Army requires the separation of men with tuberculosis from the service as soon as practicable, men are temporarily hospitalized before discharge and before their allocation to the Veterans Administration.—*Tuberculosis in the Armed Forces*, E. R. Long, Col. (MC), & E. A. Lew, Major, MAC, *Am. J. Pub. Health*, May, 1945, 35: 469.—(M. B. Laurie)

Tuberculosis in the Army.—In Switzerland the problem of tuberculosis in the army may well be divided into three phases: (1) Prophylaxis. This comprises the detection of tuberculous men prior to induction and the prompt diagnosis and exclusion from further duty of those who develop the disease while in service. (2) Treatment. The Army In-

surance System pays for the care and rehabilitation of all men who developed tuberculosis while in the service. (3) The problem of the custodial case. No adequate solution of this most important problem is in operation at this time. It is considered vital that custodial cases be given an opportunity to work and be useful during the remaining years of life instead of being condemned to years of invalidism without doing useful work. The following plan is suggested: In close connection with existing army sanatoria, yet separate from an administrative point of view, settlements are to be constructed. Here the chronically active, quiescent or custodial cases live together in small houses in homelike surroundings free from the rigid restrictions of sanatorium life. Work tolerance is determined by the physician who is the only link between the sanatorium and the settlement. This facilitates medical supervision and readmission to the sanatorium if and when this becomes necessary. The Army Insurance System cannot undertake the financial support of these settlements, but it is believed that public funds should be made available for this purpose. The average Swiss citizen is thereby given a chance to pay off a debt of gratitude to those who became hopelessly ill in the service of their country.—*Tuberkulose und Armee im Aktivdienst 1939 und in den folgenden Jahren*, M. Voute, Schweiz. med. Wchnschr., July 22, 1944, 74: 786.—(H. Marcus)

Tuberculosis in Amazon Region.—A comparative study of the number of deaths caused by malaria and tuberculosis carried out in Manaus, capital of the Brazilian estate of Amazonas, showed that, from 1922 to 1943, 4,952 people died of tuberculosis and 7,871 of malaria. The percentage in relationship to the total death rate was 21.41 for malaria and 13.47 for tuberculosis. The figures per year show an increase in the tuberculosis mortality and a decrease in the malaria mortality. The data are subject to several sources of error. The average rate of mor-

tality caused by tuberculosis in the last five years was the following in some Brazilian cities:

- 1st—Vitoria: more than 500 per 100,000 inhabitants
- 2nd—Salvador: more than 500 per 100,000 inhabitants
- 3rd—Recife: more than 441 per 100,000 inhabitants
- 4th—Manaus: more than 422 per 100,000 inhabitants
- 5th—Belem: more than 388 per 100,000 inhabitants
- 6th—Portoalegre: more than 373 per 100,000 inhabitants
- 7th—Rio: more than 322 per 100,000 inhabitants

The influence on tuberculosis of the diseases prevalent in that region is studied. Tuberculosis, which was brought from Europe to this region, spread rapidly in this part of the country, favored by economic factors, underfeeding, climate, etc. So far, despite the efforts made by the Liga Amazonense contra la Tuberculose, very little has been accomplished in the fight against the disease in the Amazonas.—*Tuberculose no Amazonas, D. Batista, Rev. brasil. de tuberc., July-August, 1944, 94: 203.*—(P. B. Franca)

Fight against Tuberculosis in Brazil.—Tuberculosis did not exist among the Brazilian Indians when the country was discovered, but was introduced by the first European settlers. The disease spread rapidly and has been a subject of great concern to the government. In 1941 the National Service of Tuberculosis was established; its chief purposes are to study the problems related to tuberculosis, to organize prophylaxis, to supervise the governmental and private institutions devoted to the fight against tuberculosis, etc. In the first three years of its existence this service built and inaugurated several sanatoria, with a total of 2,030 beds; three other sanatoria, with a total of 800 beds, were built but are not yet open; other sanatoria with a total of 1,980 beds are

being built. Other details of the organization are given.—*Servico nacional de tuberculose, S. Libanio, J. d. clin., August, 1944, 8: 259.*—(P. B. Franca)

Tuberculosis Mortality in Guayaquil.—The general death rate in the City of Guayaquil in recent years has been extremely high. The tuberculosis death rate is very high. In the ten-year period from 1932 to 1941, 8,064 residents of the city died from tuberculosis. The death rate for tuberculosis rose from 486.5 in 1932 to 655.0 in 1941. These figures are comparable with those of London in 1740 and Edinburgh in 1793. The city is in that phase known in tuberculosis epidemiology as the "phase of massive tuberculization" (Sayé) or "epidemic" (Hofbrauer). The highest mortality from tuberculosis is at the age of 20 to 24 years. The mortality from tuberculosis in relation to the general mortality between 1932 and 1941 was between 15.64 per cent (1932) and 20.00 per cent (1937). The death rate in different age groups is almost the same in males and females. Deaths from extrapulmonary tuberculosis in relation to pulmonary tuberculosis were 24.5 per cent in 1934 and 9.1 per cent in 1941. This decrease in the extrapulmonary forms is probably due to the increasing use of pasteurized milk. Tuberculosis was the principal cause of death from 1932 to 1939, when it ceded the first place to the diarrheas and enteritis, not by a decrease of the former, but by an increase of the latter.—*Statistical Study of the Tuberculosis Mortality in Guayaquil, Ecuador (South America), J. A. Higgins, Rev. Ecuatoriana de hig. y med. trop., January, 1944, 1: 34.*—(G. C. Leiner)

Tuberculin.—Four factors are important in the evaluation of tuberculin skin tests: (1) way of testing; (2) amount of tuberculin used; (3) interpretation of reactions; (4) strength of tuberculin. Nineteen different tuberculins were tested and were found to vary so greatly in their strength that the necessity to arrive at a standardization in order to

obtain comparable results appears to be of utmost importance. The "Tuberculin Unit" which is the unit of weight corresponding to 0.01 mg. of the "Old Tuberculin" prepared by the Serologic Institute in Copenhagen is accepted as standard. The Mantoux reaction is superior to all other procedures, if it is carried out correctly. Out of 366 children thus tested 92 had a positive skin test after the first dose, 33 responded to the second and 10 to the third injection.—*Tuberculines et réactions tuberculiniques*, P. Hauduroy, *Presse méd.*, January, 1945, 2: 13.—(G. Simmons)

Tuberculosis in Infant.—The development of the primary complex is the most serious problem of the infantile organism. If all the defenses of the organism work well the primary focus will be prevented from breaking down. But if the bacilli intrude further than the primary complex, a general infection by lymphatic, bronchogenic or hematogenic ways will take place. Transition forms between the benign and the malignant childhood type of tuberculosis exist. A change from a primary benign type to a malignant type can be detected in X-ray series only because the infiltrate in the beginning looks alike in both forms. There are several causes which determine whether the primary infection will be benign or malignant: (1) The age of the child. The caseous pneumonic and bronchopneumonic forms are more frequent in the first than in the second year of life and even more frequent in the first six months. (2) The virulence of the bacilli. (3) The intensity and repetition of the contact. Massive repeated exposures to contacts, that is, family contacts, give a poorer prognosis than sporadic contacts. (4) Hygienic and nutritional factors. Breast-fed infants offer a better resistance than artificially fed, unless the mother is the source of the infection. (5) Intercurrent diseases. Measles, whooping cough, influenza, malaria convey to the child an anergy to tuberculosis. (6) The non-specific resistance of the organisms in relation with hereditary factors. The author gives the *intra vitam* and autopsy findings of 30

cases of tuberculous caseous pneumonia and bronchopneumonia which have to be considered as primary infections. The age of the children at their deaths was between 3 months and 30 months. The average duration of the disease was three and a half months. It is rare to find purely pneumonic or bronchopneumonic lesions. Generally mixed lesions are found at autopsy. The caseous pneumonia extends over the entire lobe. It may progress from the primary complex, but sometimes it has no direct relation to it. An exacerbation of the glandular focus may give rise to a postprimary or secondary infiltrate which can develop into a malignant progressive form of tuberculosis. The clinical aspect may be that of a pneumonia with high fever, dyspnea, cough and signs of hepatization of the lung. Or the disease may come on insidiously with anorexia, subfebrile temperature, disturbances of the digestive tract and absence of physical findings. The appearance of erythema nodosum is pathognomonic. Both forms develop cavities and death occurs from cachexia, miliary tuberculosis or meningitis within one to six months. The X-ray film shows triangular shadows in one or more lobes radiating from the hilum or band-like densities extending from the hilum towards the axilla. Later on, when the caseous process is well advanced typical cavities can be seen. The caseous bronchopneumonia is an acute lesion which affects both lungs and leads rapidly to death. It may start like a banal bronchopneumonia. The only difference is the persistence of the foci, the long duration and the rapid deterioration of the general condition. Death occurs from within days to a few weeks, generally from cachexia. In some cases the beginning of the disease is masked by slight temperature, anorexia, diarrhea, anemia and loss of weight. This condition may last for months. Only X-ray and sputum findings may allow the exact diagnosis. The X-ray film shows always a great number of smaller or larger hazy spots, isolated or in groups. When these spots coalesce and soften a cavity forms. This is much more frequent than is generally

thought. The cavity in itself does not lead to death. Hemoptysis and spontaneous pneumothorax are very infrequent in infants, although the cavities are very large and generally subpleural. Therapeutic pneumothorax, although very difficult to institute, should always be tried. But generally the treatment does not succeed. There is strong evidence that certain infants present a natural specific resistance to the spread of the disease.—*Formas caseosas de la tuberculosis del lactante*, J. R. Betancourt, *Rev. cubana de tuberc.*, July–September, 1944, 8: 495.—(W. Swienty)

Negative Tuberculin Tests in Children.—The problem of negative skin tests in children, who previously had reacted positively to the injection of tuberculin, was studied in 745 children of the age group 5 to 15. Skin tests were repeated every three months. In 17 of the children the previously positive skin test turned negative and the following causes for this phenomenon were found: (1) The first group of such children did not show any evidence of clinical or radiological tuberculosis and it is therefore assumed that these children had had a very slight infection which did not result in a primary focus. (2) In a second group of children the previously positive skin test became negative and stayed negative for some time until it turned positive again. Here the presence of healed lymph nodes was noted and it is admitted that a reinfection had occurred. (3) The third group was composed of 2 cases of pleurisy and 2 patients with active pulmonary tuberculosis with poor prognosis. It is admitted, however, that differences may exist between the general sensitivity of the organism and that of the skin.—*Les éclipses cutanées à la tuberculine chez l'enfant*, Bergeron, André, Bucquoy & Beust, *Presse méd.*, 1942, 11: 553.—(G. Simmons)

Cavernous Tuberculosis in Infant.—The remarkable case of an infant in whom the diagnosis of pulmonary tuberculosis was made on the basis of positive sputum examinations at the age of seven months is reported. X-ray films revealed a giant cavity in the

upper part of the right lower lobe; ten months later the cavity had disappeared. The child was subsequently followed for eight years during which time physical examinations and X-ray films remained persistently negative.—*Guérison, contrôlée pendant 8 ans, d'une caverne pulmonaire géante apparue chez un nourrisson tuberculeux de 7 mois*, R. Turpin & P. Chassagne, *Rev. de la tuberc.*, 1942, 7: 42.—(G. Simmons)

Primary Tuberculous Infection.—Inasmuch as it is difficult or impossible for tuberculosis institutions to hire only tuberculin-positive personnel, it has been the practice at the Cheshire Joint Sanatorium to employ tuberculin-negative personnel as well. Nurses and maids frequently hail from rural districts or from Ireland, and among them are a large number of non-reactors. It has been found impracticable and impossible to protect these people from infection, and therefore a system has been worked out whereby these people are given maximal supervision and care during the period of their primary infection. All employees have a thorough examination on entrance. This includes physical examination, taking of weight, sedimentation rate, chest X-ray and, of course, tuberculin test. All these tests are repeated at monthly intervals, except for X-raying, which is repeated every three months until Mantoux conversion. The cases naturally fall into four groups. *Group 1:* Mantoux conversion without X-ray evidence of a primary complex, without signs and symptoms of disease, and with a normal sedimentation rate. These cases continue to work, and they are observed for three months. *Group 2:* Asymptomatic cases, without evidence of hilar lymph node enlargement, but with elevated sedimentation rate. These cases are put on half duty for one month, and after that on full duty, and observed for three months, providing that the sedimentation rate becomes normal after the first month. *Group 3:* Asymptomatic, but with X-ray evidence of hilar enlargement, with or without primary complex. These patients are given bed-rest for one month, half duty for

three months, full duty thereafter provided that the nodes show satisfactory retrogression. *Group 4:* Those clinically ill and/or showing radiological signs other than a retrogressive primary complex. These cases are treated as long as indicated. Of a total of 340 new entrants, 72 were tuberculin-negative. Forty-eight out of these 72 showed Mantoux conversion. Thirty-three belonged in groups 1 and 2, 5 in group 3, and 9 in group 4. One case showed evidence of reinfection type of tuberculosis. Of the 10 cases that developed tuberculosis, all are well at this writing, and 7 of the 10 have been observed for a five-year period. None of the tuberculin-positive entrants developed tuberculosis within the seven-year period of this study.—*Primary Tuberculous Infection in a Sanatorium Staff*, P. W. Edwards & A. C. Penman, *Lancet*, April 7, 1945, 248: 429.—(H. Marcus)

Work in Tuberculosis.—The value of graduated exercise in the treatment of tuberculosis was not appreciated until Paterson put his views into effect between 1910 and 1916. Paterson's exercises were rigid and monotonous and lacked the stimulus of productive work. At Papworth, Sir Pendrill Varrier-Jones recognized the great psychological advantages of productive and profitable employment, but medical supervision was insufficient at times and the capacities of patients were incorrectly assessed. From these earliest experiments stem our present-day methods which recognize the need for productive work more than for diversional activities, and thus demonstrate the superiority of rehabilitation over simple occupational therapy. The patient is discharged cured only when, in addition to regaining his health, he has also made a new adjustment to normal life by learning an occupation which is compatible with his health. Employment of patients in sanatoria is urged, or in sheltered industries. Those that cannot be accommodated in this fashion should receive modified employment in normal industry.—*The Value of Work in Treatment of Tuberculosis*, F. Heaf, *Lancet*, March 3, 1945, 248: 263.—(H. Marcus)

Chest X-ray Examination.—The "hard", recumbent X-ray examination of the chest sometimes overcomes difficulties which are present in the routine views. The following technique is advised: "The patient lies flat on his back on the horizontal table with a Potter-Bucky diaphragm. The X-ray tube is brought into position and centered more or less on the middle of the body of the sternum. The distance is thirty inches. Other factors are 60 K. V., 90 M. A. and 1 second." The following results are obtained: (1) Pleural fluid spreads out. (2) Breasts flatten out. (3) The mediastinal structures are very well seen. (4) The bony thorax and its abnormalities are seen more clearly. (5) The position of the left diaphragm is marked by putting barium into the stomach. Cases are presented which show the advantages of this method.—*The Value of the "Hard" Recumbent X-ray Examination of the Chest*, S. F. Oosthuizen, *Clin. Proc. (Cape Town)*, January-March, 1945, 4: 11.—(G. C. Leiner)

Lower Lung Field Tuberculosis.—Two thousand consecutive cases discharged between February, 1933 and February, 1942 were studied by X-ray. Cases were excluded for the following reasons: (1) infiltrations in the upper half of either lung, (2) primary tuberculosis, (3) bronchiectasis, (4) pleural effusion, and (5) pleural thickening unless concomitant parenchymatous tuberculosis was present. Of 2,354 cases discharged from the medical service of the Robert Koch Hospital, St. Louis, during the above period, 63, or 2.7 per cent, satisfied the above criteria. The incidence of basal tuberculosis as reported in the literature varies from 0.003 per cent to 18.3 per cent. The authors account for this wide variation on the basis of the type of sanatorium in which the studies were made. They suggest that the low figures come from large municipal sanatoria where patients are usually seen first in an advanced stage, while the higher incidence is reported by authors working with smaller and more select groups seen in earlier stages before spreads to the upper lung fields have occurred.

The sex distribution was two females to each male hospitalized in the same hospital for tuberculosis during the same period. There were 44, or 69.8 per cent, females, and 11, or 30.2 per cent, males. These findings are in agreement with the general preponderance of females to males noted in studies of lower lung field tuberculosis. There was no definite relationship so far as race was concerned. It was noted that 91.5 per cent of the cases occurred in patients under 40 years of age. However, in Negroes, 90 per cent of the cases were under 30 years of age. This is also in accord with findings reported in the literature. Of the basal lesions 58.7 per cent were present on the right side as contrasted to 41.3 per cent on the left side. In a consideration of stage of disease in the group with lower lung field tuberculosis and in the balance of the tuberculous hospital population, the following figures were found: 61.9 per cent far advanced in the basal group as contrasted with 72.9 per cent in the general group, 38.1 per cent moderately advanced in the basal group as contrasted with 22.6 per cent in the general group, and no minimal cases of lower lung field tuberculosis while there were 4.4 per cent of minimal cases in the general group. The authors account for the absence of a minimal group among those with basal tuberculosis on the basis of lack of recognition of minimal lower lung field tuberculosis. There was no essential difference in pathology nor symptomatology, except that there was a history of hemoptysis in 75 per cent of those with basal tuberculosis. Various collapse procedures were used. Of 4 cases treated by thoracoplasty, only one became arrested and, in that patient, the operation was begun with the lower ribs and carried upward. Approximately one-third of the group were arrested at the time of discharge, one-third died, and one-third left improved, quiescent or unimproved. These findings at discharge parallel those in other cases of pulmonary tuberculosis discharged from the Robert Koch Hospital.—*Lower Lung Field Tuberculosis*, S. S. Romendick, B. Friedman & H. F.

Schwartz, *Dis. of Chest*, November–December, 1944, 10: 481.—(K. R. Boucot)

Prephthistical Tuberculosis. — The term prephthistical tuberculosis is applied to all tuberculous pulmonary lesions which precede the development of chronic pulmonary tuberculosis. The rôle of these lesions in the evolution of pulmonary tuberculosis is still under study. A large number of prephthistical lesions was recently discovered in mass X-ray surveys. Three criteria are given for their recognition: recently acquired tuberculin sensitiveness, recently passed simple pleurisy with effusion without parenchymal involvement, a stable X-ray lesion in the form of a round focus or a "smudge focus." Persons with any or all of these lesions continue to remain in good health over a protracted period of observation. Only very few of these lesions will progress to chronic pulmonary tuberculosis. The pros and cons of the new classification are discussed. Phthistical lesions demand immediate treatment, prephthistical lesions should be observed over a prolonged period of time. Since no adequate knowledge is available to distinguish the phthistical from the prephthistical lesions treatment will often have to be a compromise between overtreatment of the latter and inadequate treatment of the former. Individual consideration has to be given to the psychic and somatic state of the patient.—*Prephthistical Tuberculosis*, E. Mayer & I. Rappaport, *J. A. M. A.*, January 6, 1945, 127: 15.—(H. Abeles)

The term "prephthistical infiltrate" was introduced into the tuberculosis literature more than a decade ago by Ulrici. He defined it as infiltrations in the initial phase of clinical tuberculosis which have not as yet shown evidence of tissue destruction, that is, "phthistical" developments. In other words, Ulrici's "prephthistical infiltrate" is the same as the so-called "early infiltrate" before cavitation has occurred. As such, it is likely to be unstable, either progressing to excavation or regressing by absorption and/or fibrosis. [Editor]

Bronchogenic Tuberculosis.—A primary complex is found in almost every case, regardless of natural resistance or any other condition except that primary infection has taken place. Late primary infection is prone, after a short time, to cause an Assmann focus. While it is theoretically possible that these foci are due to a new "exogenous reinfection," their quick succession upon primary infection and the interposition of small, disseminated, notably apical nodules suggest that all these are manifestations of the same infection. Although about 70 per cent of primary foci sterilize themselves after some years, sterilization is less effective, and takes a longer time in calcifying postprimary foci—and it is these which are outstandingly incriminated in bronchogenic tuberculosis due to recrudescence. Another evidence of "endogenous reinfection" is the common occurrence of solitary Assmann foci in cases of disseminated tuberculosis in which all manifestations are blood-borne. Endogenous reinfection by recrudescence of calcified foci is of less importance than it used to be at a time when the majority of primary infections were acquired in childhood. Endogenous reinfection nowadays does occur from comparatively fresh primary foci. Inborn resistance decides the severity of the infection in the individual. It does not decide the type in which tuberculosis manifests itself (primary, postprimary, disseminated, bronchogenic).—*The Origin of Bronchogenic Tuberculosis in the Adult*, W. Pagel, *Brit. M. J.*, December 16, 1944, 2: 791.—(D. H. Cohen)

Generalized Tuberculosis.—An interesting case of generalized tuberculosis in a 26 year old seaman is presented. Onset was with headaches, chills and fever. During the course of the illness erythema nodosum developed. The interesting features were present in the X-ray and postmortem findings. The chest X-ray films revealed a left hilar opacity with density in the left midlung field and associated glandular enlargement. Subsequent films revealed a spread of the process on the left side and hilar involvement on the

right side. The interesting features of the postmortem examination consisted in the finding of a large breaking-down caseous peribronchial lymph node in the left side of the mediastinum—the size of a tangerine. Tuberculous pericarditis was present. There was a solitary, large tubercle found in the myocardium of the right ventricle. There were many noncaseating tubercles in the liver, spleen and kidneys. The other organs were normal. The authors conclude that the disease was a blood-stream infection with a primary focus in the peribronchial lymph node. The size of the tubercles and the absence of macroscopic caseation speak for high resistance on the part of the patient.—*An Unusual Case of Generalized Tuberculosis*, W. H. Mylechreest & I. M. Scott, *Brit. M. J.*, November 25, 1944, 2: 693.—(D. H. Cohen)

Tuberculin Therapy.—Tuberculin therapy was used in a great number of cases over a period of four years, but clinical results obtained cannot yet be evaluated. However, certain reactions were observed frequently and deserve further evaluation. There are: Acute transitory reactions. In addition to local, focal and general manifestations certain syndromes were observed which are grouped into two classes: (A) Syndromes due to fixation of tuberculin, which may be articular and range from arthralgies to true arthritides, or endocrine, manifesting themselves mainly as transient hyperthyroidism or adrenal insufficiency, or nervous, manifested by migraines, neuralgias and depressions. (B) Syndromes due to elimination of tuberculin, consisting mainly in hepatic dysfunctions ranging from a mild degree of transient hepatic insufficiency, as manifested by anorexia, nausea and indigestion, to an acute icteric state. These symptoms are definitely related to the amount of tuberculin given and to the time these injections were given. Tuberculin acts like a stimulus in the induction of a syndrome which the patient is subject to develop "spontaneously," that is, without the precipitating cause becoming manifest. The term "syndromic reaction" is suggested for

those symptoms that set in after the injection of tuberculin, that had existed some time previously and that the patient was apt to develop as a response to any adequate stimulus. The institution of an artificial pneumothorax decreases reactions to the injection of tuberculin. Tuberculin therapy is best tolerated in the absence of liver disturbances.—*De quelques incidents de la tuberculonothérapie et de leur signification*, A. Jacquelin, A. Cornet & P. Villanova, *Presse méd.*, August, 1941, No. 70/71, 884.—(G. Simmons)

Histamine in Treatment of Sweating.—Fifteen cases of pulmonary tuberculosis in which profuse perspiration was one of the most distressing symptoms were treated with intracutaneous injections of increasing doses of histamine. The initial dose of 0.1 mg. was increased daily by 0.1 mg. until the maximum dose of 10 mg. was reached. The total amount given rarely exceeded 5 mg. In 10 patients thus treated perspiration ceased, 3 patients obtained "very considerable relief," whereas in the remaining 2 patients no noteworthy results were obtained. This therapeutic effect of histamine is attributed to a block of sympathetic nerve fibres supplying sweat glands. It is not a local effect only, because histamine injected intracutaneously enters the general circulation readily. The most striking fact in this study is that histamine injected over a short period of time is able to somehow modify the function of sympathetic nerve fibres or the sweat glands for a long time, just like small doses of atropine or acetylcholine give long lasting results in relief of pain in tabetic gastric crisis and in Raynaud's syndrome, respectively.—*Histamine et sueurs*, F. Coste, M. LaMotte & G. Guiot, *Presse méd.*, March, 1940, No. 22/23, 250.—(G. Simmons)

tions are more pronounced, the hyperglycemia being only slight if the amount of glucose ingested was small and being greater if more glucose was ingested. This is interpreted as a sign of impaired liver function. The difference of glycemic values of the capillary and venous blood after ingestion of glucose is slight in normal individuals. In afebrile patients this difference is very slight, if the amount of glucose ingested is slight and is equal to or greater than that encountered in normal individuals if the amount of glucose given is great. This difference of glycemic values was always very slight in toxic patients with high fever, and this is thought to be due either to decreased pancreatic function or to a marked muscular glycogenolysis.—*Le curve glicemiche differenziali capillari-venose provocate con carico vario di glucosio nei tuberculosici polmonari in stato di grave tossiemia*, A. Baffoni, *Ann. Ist. Carlo Forlanini*, 1942, 6: 699.—(G. Simmons)

✓ **Hypovitaminoses and Tuberculosis.**—The relation between vitamin deficiencies and tuberculosis was studied in approximately 100 patients, most of them hospitalized for pulmonary and some for extrapulmonary tuberculosis. Vitamin C deficiencies were noted in 95.4 per cent of the tuberculous patients, whereas only 72 per cent of healthy individuals, kept on the same diet, had vitamin C hypovitaminosis. No relation between vitamin deficiency and pulmonary hemorrhage was noted. It was observed, on the other hand, that the deficiency increased with the progress of the pulmonary condition. No relation between gastro-intestinal disturbances and hypovitaminosis was noticed. Vitamin A deficiencies were noted in 33 per cent of the cases, whereas the percentage was higher in other patients hospitalized for diseases other than tuberculosis. This is ascribed to the fact that tuberculous patients are allowed extra butter and milk. Hypovitaminosis A was more frequent in extrapulmonary than in pulmonary tuberculosis and, contrary to what occurs in vitamin C deficiency, was always correctible by ad-

✓ **Glucose Tolerance in Pulmonary Tuberculosis.**—While in normal individuals hyperglycemic values obtained after the administration of varying amounts of glucose present only slight variations, in patients with pulmonary tuberculosis and toxemia such varia-

ministration of vitamin A. Vitamin B1 deficiency in tuberculous patients was found in 17 per cent and in other patients in 25 per cent. In all patients vitamin D deficiency was present in 23 per cent. It seems, therefore, that vitamin C deficiencies are most important and frequent in patients suffering from tuberculosis. This condition is partly due to deficient nutrition and partly to increased destruction of vitamin C, particularly in recent, progressive cases with extensive lesions.—*Tuberculosis et precarence*, H. Wasembourg, P. Boulanger, J. Swyngedauw & J. Poiteau, *Presse méd.*, 1942, No. 25.—(G. Simmons)

Postural Drainage in Pulmonary Tuberculosis.—Postural therapy has proved valuable in the treatment of 131 cases of pulmonary tuberculosis. Of 46 cases in which postural therapy only was used, the result was good in 37 per cent, moderate in 26 per cent and none in 37 per cent. Postural therapy combined with phrenic paralysis gave good results in 30 per cent of 40 cases, moderate in 28 per cent and none in 42 per cent. In combination with an ineffective pneumothorax postural therapy was effectively used in 55 per cent of 31 cases. Pneumothorax, phrenic paralysis plus postural therapy gave good results in 4 out of 6 cases and of 8 thoracoplasty cases 4 were benefited by postural therapy. Credit for improvement of the clinical condition was given to postural therapy only after previous therapy had failed. The patients were started out in a supine position, subsequently the foot of the bed was raised from 20 to 30 cm. up to 60 cm. This postural therapy was maintained from three months up to more than a year, with an average of six to eight months. There are no special contraindications. Best results are obtained in recent cases and particularly in conjunction with a phrenic paralysis. In hypotensive patients the condition may grow worse. Postural therapy, it is concluded, should be used in all those cases in which the process of retraction is to be reinforced.—*La declivoterapia nel trattamento della tbc. polmonare*, F. Tullini,

Riv. di pat. e clin. d. tuberc., 1943, Vol. 16.—(G. Simmons)

Tomography and Anatomical Findings.—In a patient who died of advanced pulmonary tuberculosis a series of tomographs was taken shortly after death and the X-ray findings compared with the autoptic material, which was frozen and then sectioned *in toto*. Thus each anatomical lesion could be compared with the picture obtained tomographically. The series of five tomographs and corresponding anatomical sections are presented in this paper. In two tomographs there appeared to be a small pneumothorax pocket, which anatomically, however, proved to be emphysematous lung tissue. A small cold abscess of a rib failed to become evident tomographically.—*Indagini comparative tra stratigrafia e reperti anatomici polmonari*, C. Panà & G. Torelli, *Ann. Ist. Carlo Forlanini*, 1942, 6: 687.—(G. Simmons)

False Cavitory Images.—Two cases demonstrating how false cavitory images may be due to abnormalities or superposition of images of normal pulmonary structures are presented. In the first case a multiloculated cavity was seen in the postero-anterior view, but no evidence of a cavity could be found on lateral views or on tomographs. The false image was due to a bony defect caused by an old bullet wound of the chest, which had produced fracture and subsequent abnormal osseous regeneration of a rib of the anterior and posterior aspect of the chest. In the second case a cavitory image with an apparent fluid level could not be detected on lateral views and tomographs proved that the image was due to vascular markings.—*A propos de deux images de fausses cavernes*, R. Pruvoist & Tiret, *Presse méd.*, February, 1942, No. 17, 211.—(G. Simmons)

Tuberculous Cavities.—Bacteria in tuberculous cavities in cadavers were studied. Ordinary bacteria, such as staphylococci, pneumococci and streptococci, were found in the purulent secretion covering the cavity

wall. In the cases of old cavities, tubercle bacilli were not found, whereas their presence was constantly revealed in fresh cavities. In the cavity wall itself, on the other hand, only tubercle bacilli, without secondary infection, were found. Regarding these findings, it is worth noting that secondary infection of the tuberculous tissue itself is rarely found; tuberculous tissue therefore seems to be particularly resistant to nontuberculous infections. This explains the very rare coexistence of tuberculosis and abscess of the lung.—*La flora microbiana de las cavernas tuberculosas pulmonares*, A. A. Raimondi, R. Scartaschini & F. M. Gonzalez, *Arch. argent. de fisiol.*, October-December, 1944, 20: 367.—(H. Behm)

Tuberculosis in Twins.—The case history of two 48 year old mono-ovular twins is reported. Both had tuberculosis of the left kidney and bilateral tuberculous epididymitis. One of the twins developed epididymitis and renal tuberculosis at the age of 46, the other developed epididymitis at the age of 25 and tuberculosis of the kidney at 38. In both cases the tuberculosis of the kidney had started at the upper pole. The twins had lived in the same environment up to the age of 17.—*Urogenitaltuberkulose bei eineiigen Zwillingen*. Erbarzt, C. H. Schroeder, *München. med. Wchnschr.*, 1941, 9: 217.—(G. Simmons)

Diasone.—The studies of a number of workers have shown that diasone has its place in the treatment of experimental and possibly clinical tuberculosis. It is stable and water soluble if protected from oxidation in vacuum glass ampules. Exposed to the air, an aqueous solution after a few minutes turns cloudy. Later a precipitate is formed because of the combined effect of carbon dioxide of the air and the oxidation of diasone, resulting in an increase of the acidity of the solution. By the addition of sodium bicarbonate or sodium hydroxide, the precipitated diasone can be redissolved. If diasone powder is exposed to air for several days part of it turns insol-

uble. Mixing diasone and solid sodium bicarbonate (9:1) maintains diasone unchanged and water soluble for a long period of time, provided it is kept in tightly closed bottles. Gastric juice normally containing from 0.4 to 0.5 per cent hydrochloric acid may act upon diasone, but it was proved by tests that in two hours 0.4 per cent hydrochloric acid at 37°C. causes neither the splitting off of formaldehyde sulfoxylate nor the liberation of diaminodiphenylsulfone. Diasone is sufficiently pure and uniform to be satisfactory in treating infected animals and human beings as well. This drug can be quantitatively estimated by diazotization and subsequent formation of a dye, according to a modification of a method of Bratton and Marshall. The chronic and acute toxicity of diasone tested orally and intravenously on mice, rats and rabbits is noticeably less than that of most well known sulfonamides, including sulfadiazine. It is far less toxic than diaminodiphenylsulfone. Diasone has shown high therapeutic effectiveness in mice infected with beta-hemolytic streptococcus as well as type II pneumococcus infection. At the present time, diasone is being investigated clinically in the treatment of tuberculosis.—*Diasone: Its Toxicity and Therapeutic Effectiveness*, G. W. Raiziss, M. Severac & J. C. Moetsch, *J. Lab. & Clin. Med.*, April, 1945, 30: 317.—(F. G. Petrik)

Action of Extracts of Penicillium upon Experimental Tuberculosis.—Products of different species of *Penicillia* were tested from the point of view of their bacteriostatic action on tubercle bacilli *in vitro*, of their inhibitory action upon the formation of the tubercle in the chorio-allantoic membrane of the chick embryo, and of their chemotherapeutic action on the experimental tuberculosis of the guinea pig. Penicillin and Penatin did not prevent the growth of tubercle bacillus *in vitro*. Aqueous solution of the ethereal extract of *P. notatum* Ravlin Thom. showed *in vitro* marked activity in certain concentrations; similar extracts of *P. cyclopium* were inactive under the same conditions. All the preparations tested proved to have some inhibitory

action on the formation of tubercles in the chorio-allantoic membrane, but did not show a reduction in the incidence of the infection. Neither penicillin (Florey) nor extracts of the culture media of *P. cyclopium* showed any activity against experimental tuberculosis in guinea pigs. Very little results in this respect were obtained with extracts of culture media of *P. notatum* Rawlin Thom.—*A Acao dos extractos de penicillium na tuberculose experimental*, M. I. Smith & E. W. Emmart, *Rev. brasil. de tuberc.*, September-October, 1944, 95: 331.—(P. B. Franca)

Broncholithiasis.—In a patient subject to recurrent attacks of bronchitis with bloody expectoration, broncholithiasis is to be considered. Expectoration of calcified portions of lymph nodes, or even pulmonary foci, may be protracted over a number of months or years. The individual stones may be so small as to be missed entirely unless the condition is suspected and the patient is instructed to look for them. In its symptomatology the condition closely resembles Castellani's bronchospirochetosis. The sputum will frequently contain a sufficient number of spirochetes from the mouth so that examination of the sputum obtained by bronchoscopic aspiration is essential. Bronchoscopy usually shows a nonspecific inflammation with ulceration and granulation tissue at the point of the breakthrough. Two cases are presented. One was temporarily bettered by a course of arsenicals thereby adding to the difficulty in differentiating the disease from bronchospirochetosis. Neither case developed evidence of tuberculous spread during the time of observation, nor was there any evidence of active tuberculous disease.—*Ueber zwei Fälle von Broncholithiasis. Zur Differentialdiagnose der Bronchospirochaetosis Castellani*, E. Zweifel, *Schweiz. med. Wchnschr.*, August 5, 1944, 74: 833.—(H. Marcus)

Bronchial Stenosis.—Tuberculosis is a frequent cause of bronchial stenosis. A careful history and physical examination, X-ray and bronchographic studies and laboratory

investigations are of great help in establishing the diagnosis of bronchial stenosis. Bronchoscopy, especially if completed by biopsy, is decisive in corroborating and specifying the diagnosis. In the sanatorium of Huipulco bronchoscopy is a routine examination before and after thoracoplasty, in cases with positive sputum with no evidence of parenchymatous lesions, in cases of hemoptysis without evidence of pulmonary disease, and finally in the presence of bronchial stenosis. In 207 bronchoscopies, 58 cases of bronchial tuberculosis were found. Four cases are reported, illustrating some of the possible causes of bronchial stenosis besides tuberculosis, such as, syphilitic mediastinitis, traumatic lesions affecting the bronchi or peribronchial structures, nonspecific bronchopulmonary processes.—*Contribucion al estudio de la estenosis bronquial*, J. C. Villegas, *Rev. mex. de tuberc.*, December, 1943, 5: 165.—(L. Molnar)

Hemorrhagic Tracheobronchitis.—Hemorrhagic tracheobronchitis, diagnosed in several cases, is considered secondary to lymph node tuberculosis, itself secondary to an active or inactive pulmonary focus. Tracheobronchial hemorrhages may occur in all phases of pulmonary tuberculosis. These hemorrhages are scant, the blood is red and without foam. The patient's general condition remains good, there is no elevation of temperature and the physical examination is, as a rule, negative. In women such hemorrhages frequently occur during menstrual periods. Bronchoscopically one sees small areas with ill defined borders, where the mucosa is thickened, infiltrated, highly hyperemic. In a later stage these areas become sclerotic and newly formed vessels become apparent. Sometimes such foci are multiple, but as a rule they are isolated and are most frequently found just above or below the carina. They are in relation to an inflammatory process of the airways secondary to tuberculosis of adjacent lymph nodes.—*Trachœobronchite hémorragique et tuberculose ganglio-pulmonaire*, A. Dufourt & P. Mounier-Kuhn, *Presse méd.*, January, 1943, No. 3, 26.—(G. Simmons)

Pathological Granulations in Leucocytes.—Although the occurrence of so-called toxic or pathological granulations in neutrophil leucocytes in the course of various infectious diseases and intoxications has been known for some time, only recently Benda started a study of this granulogenesis in its relationship to tuberculosis. It was found that in tuberculous patients these granulations, once established, are a permanent feature and present modifications paralleling the clinical course of the disease in man. The amphophil granulations, which normally are very fine and are equally distributed in the clear protoplasm of neutrophil leucocytes, are, under pathological conditions, bigger, irregular, agglomerated at the periphery of the cell and appear in larger numbers. The leucocytes are increased in size. According to the number and volume of the granulations, the leucocytes are divided into three groups: (1) type $G++$, the extreme type; (2) type $G+$, the medium type; and (3) type $G\pm$, the intermediate type. Frequently the predominance of either type is evident; sometimes, however, more types coexist in the same individual and the predominance of either type must be expressed in percentage. The granulogram $\frac{(G++)+(G+)+(G\pm)}{GN}$ expresses the rela-

tion between the different types of abnormal leucocytes and the normal leucocytes. Such granulations can be produced artificially by injecting experimental animals with pathological material such as sputum and pleural fluid; the type of granulation observed is then dependent upon the virulence of the injected material. In all cases of reinfection tuberculosis in which bacilli can be found easily and persistently, the granulations are constantly present. Most frequently type $G++$, very often type $G+$ is observed, whereas type $G\pm$ was never found. In arrested cases and in cases of primary tuberculosis with persistently negative sputum the granulations are frequently of the intermediate type $G\pm$. In patients suffering from conditions other than tuberculosis, the granulations remain normal. This is true for certain conditions

that are important for the differential diagnosis of tuberculosis (acute pneumococcal pneumonia, acute rheumatic fever, subacute bacterial endocarditis, bronchogenic carcinoma, leukemia etc.). In 3 cases of leprosy and in 3 cases of Hodgkin's disease the granulations remained normal, too. In typhoid fever the granulations are frequently of the $G+$ type but their appearance is only temporary. In one case of Besnier-Boeck's disease the granulations were of the intermediate type, but showed daily variations. After inoculation of pathological material (sputum, pleural and spinal fluid) into guinea pigs characteristic changes in the granulations occur. Between the tenth and fifteenth day after the injection of material, negative microscopically, but obtained from a tuberculous patient, characteristic changes in the granulations occur. They become of the $G\pm$ and later $G+$ or even $G++$ type. It seems, therefore, that the type of granulation observed in the animal eventually is identical with that of the patient whose material was inoculated. If the animal is inoculated with an attenuated strain, $G\pm$ granulations can be seen, which, however, disappear after a certain time. If dead bacilli or their lipid or fatty constituents, or if other than acid-fast bacilli are injected, no changes in the leucocytes occur. Blood (or serum) of tuberculous patients, injected into guinea pigs, induces the same granular changes as sputum, pleural fluid etc., and here again the amount of granulations thus induced is related to the degree and the evolution of the disease, whereas blood (or serum) from healthy individuals or from patients suffering from conditions other than tuberculosis does not induce any changes in the morphology of leucocytes. If serum or blood, capable of inducing granulations, is filtered through a Chamberland filter No. 5, no modifications are induced, or if they do occur their appearance is greatly delayed and they do not correspond to changes induced by the same material in unfiltered state. The finding of type $G+$ or $G++$ granulations in man is therefore very suggestive of tuberculosis, whereas a normal

granulogram eliminates, at least temporarily, the diagnosis of tuberculosis. $G \pm$ granulations are found in arrested or initial cases of tuberculosis. The granulodiagnosis may be important in the screening of suspected individuals, in the differential diagnosis of pneumonia and in the examination of pathological material, such as pleural fluid and sputum. The changes observed are by no means pathognomonic, but importance is attached to these findings for the diagnosis and the prognosis of tuberculosis. It seems that blood from tuberculous patients, only exceptionally containing bacilli, nevertheless does contain a substance capable of modifying the granulations contained in neutrophil leucocytes of guinea pigs.—*Les granulations "pathologiques" des polynucléaires neutrophiles chez les tuberculeux et au cours de la tuberculose expérimentale du cobaye*, J. Niclas, *Pressc méd.*, February, 1942, No. 17, 213.—(G. Simmons)

Anemia in Pulmonary Tuberculosis.—Of 150 patients with different forms of pulmonary tuberculosis a varying percentage of 15 to 50 per cent (different percentages were encountered in the different groups in which the patients were divided according to the type of disease and its stage) showed anemia of the hyperchromic type with a color index greater than 1. This type of anemia, which however could be differentiated morphologically from the pernicious type, was observed only in stationary cases. In mild and in severe progressive cases the anemia was always hypochromic. It is believed that anemia in these cases is due to a toxic effect on the bone marrow rather than to hemolysis.—*Contributo alla conoscenza delle alterazioni ematologiche nella tubercolosi polmonare*, M. Nuti, *Ann. Ist. Carlo Forlanini*, 1942, 6: 3.—(G. Simmons)

Bilirubinemia in Tuberculosis.—In febrile and progressive cases of pulmonary tuberculosis bilirubinemia increases. It decreases and turns normal as the disease regresses. Where there are associated intestinal dis-

turbances, the bilirubinemia is persistently elevated. In pulmonary tuberculosis associated with syphilis, the bilirubinemia is very high. In stages of anergia, the bilirubinemia returns to normal limits.—*Bilirubinemia fisiologica e bilirubinemia nei vari quadri di tubercolosi polmonare*, A. Cimino, *Ann. Ist. Carlo Forlanini*, 1942, 6: 252.—(G. Simmons)

PH of Intracavitary Contents.—The PH of the intracavitary contents is acid and turns alkaline during a successful intracavitary aspiration process. The aspiration, it is believed, causes a flow of liquids from the periphery toward the interior of the cavity. These liquids play an important part in the improvement of cellular metabolism.—*Il comportamento del PH nei liquidi endocavitari durante il trattamento aspirativo*, G. Zirilli, *Ann. Ist. Carlo Forlanini*, 1942, 6: 267.—(G. Simmons)

Glycolysis in vitro in Tuberculosis.—Glycolysis, studied *in vitro*, in the blood of tuberculous patients was found to be increased as compared to that of the blood of healthy individuals. The increase is proportionate to the degree of toxemia.—*La glicolisi in vitro studiata in rapporto alla tossemia tubercolare*, A. Baffoni, L. Rupoli & M. Spadoni, *Ann. Ist. Carlo Forlanini*, 1942, 6: 53.—(G. Simmons)

PH of Pleural Fluids.—Clear pleural fluid complicating a pneumothorax has an alkaline reaction very near that of the blood. Fluids from empyemata, however, are acid. The acid reaction becomes less pronounced and eventually may turn alkaline as the case becomes chronic. It is believed that the reaction depends not only on the number of pus cells, but particularly upon the presence of metabolic processes and metabolic exchanges that take place between the fluid and blood.—*Il comportamento del PH nei liquidi parapneumotoracici semplici e purulenti*, G. Zirilli, *Ann. Ist. Carlo Forlanini*, 1942, 6: 10.—(G. Simmons)

Patch and Mantoux Tests in Dermatoses.—

Despite an occasional contradictory report the consensus seems to be that the patch method of testing is efficient and compares favorably with the intracutaneous technique in detecting skin sensitiveness to tuberculin. These conclusions were arrived at by testing healthy persons and those suffering from nontuberculous internal disease. There are no reports in which the efficacy of the Mantoux and patch test techniques in tuberculous and nontuberculous dermatoses are compared. Two hundred patients with various dermatological diseases were tested with tuberculin employing the intracutaneous and patch methods simultaneously. Twenty-four of these patients were suffering from various tuberculoderms. A high degree of uniformity in the incidence of positive reactions to the Mantoux test with Old Tuberculin, the patch test with Old Tuberculin and the Vollmer patch test (used in 167 cases) was found. Some disparities occurred, the cause of which remains unknown. There was no significant difference observed between the appearance of the patch test reactions in patients with tuberculoderms and in those with nontuberculous eruptions. It should be noted, however, that in 2 patients with lupus vulgaris the reaction at the site of the patch test was so severe as to cause considerable discomfort. It follows that in the presence of a tuberculoderm associated with a high sensitiveness to tuberculin (tuberculosis luposa, verrucosis cutis and verrucosis colliquativa) the use of patch tests with full strength Old Tuberculin, as is ordinarily employed, is not advisable.—*Tuberculin Patch Test and Mantoux Test: Comparative Study in Cases of Various Dermatoses, Including Tuberculoderms, F. Pascher & M. B. Sulzberger, Arch. Dermat. & Syph., April, 1944, 49: 256.*—(J. S. Woolley)

Sensitivity to Tuberculin in Acne.—The possibility of a relationship between acne and tuberculosis has interested many observers. The present report considers the Mantoux reactions of a large number of university students with and without acne. Tests were

made with the 1:10,000 dilution of tuberculin, and if a reaction did not appear, with the 1:100 strength. Of 13,748 students, 3,549 reacted to tuberculin. Eight hundred and eighty-nine of the latter had acne. In this group the incidence of positive skin-tests was 22 per cent, in contrast to 27 per cent in the no acne group. The author considers this difference to be of statistical significance.—*Lessened Sensitivity to Tuberculin in Acne, T. W. Lynch, Arch. Dermat. & Syph., March, 1944, 49: 174.*—(J. S. Woolley)

Transplacental Tuberculous Infection.—

The transmission of tuberculosis from the mother to the fetus was studied experimentally. Twelve rabbits were subcutaneously inoculated with avian tubercle bacilli. Blood cultures were made during pregnancy and in the litter, after delivery. The avian tubercle bacilli produce a chronic type of tuberculosis, which permits the rabbit to live up to twelve months, and in this way several successive gravidities could be observed. It has thus been possible to study the transmission of the bacilli during various different stages of the disease in the mother. Positive transplacental transmissions of avian bacilli to the fetus were shown in 36.66 per cent, most of which took place between the third and sixth month of the disease, in other words, when it was at its apex. In 60 per cent of the positive cases, bacilemia in the mother was also recorded, whereas they were not found in any of the negative cases. According to these findings, the placenta is apparently subject to periodic discharges of tubercle bacilli, which, when repeated with intensity, makes the placenta permeable to the bacilli. The passing through of the bacilli preferably takes place during the second half of pregnancy, when the histological layers of the placenta become thinner, and the enzymatic capacity of the cells decrease. On the other hand, it may be deduced, from the study of the tuberculous rabbits which were pregnant several times, that pregnancy does not seem to aggravate pulmonary tuberculosis in the mother. Attention is also called to the small proportion

(3.63 per cent) of abortions and premature deliveries in this experimental study. In a second series of studies, 26 guinea pigs were inoculated intracardially with avian bacilli, and were killed shortly thereafter. In these cases acute tuberculosis was obtained. There were 53.85 per cent of transplacental transmissions, and tubercle bacilli were found in the fetal organs and in the amniotic fluid as early as thirty to sixty minutes after inoculation. The fact that, in spite of the existence of tuberculosis of the placenta in 100 per cent of the cases, only half of the fetus were found to be infected shows that this has not been a mere mechanical outflow of the bacilli through the placenta. On the other hand, according to findings of other observers, a great majority of the transplacental transmissions of germs take place in the presence of a normal placenta. Transmission is therefore due to the virulence itself of the microbe. It is noted that tuberculous microscopic lesions were not found in any of the fetus which were positive in the bacteriological investigation. This discrepancy is probably due to the low ability to react of the fetal organs, when confronted with the tubercle bacilli.—*Pasaje transplacentario del bacilo de Koch, estudio experimental*, H. V. Vaccaro & L. Paredes, *Ap. respir. y tuberc.* (Chile), January-March, 1945, 10: 11.—(H. Behm)

Sterilization of Tuberculous Lesions.—Sterilization of tuberculous lesions and loss of tuberculin sensitivity, as can be observed in man, never occur in the guinea pig, because tuberculosis in the guinea pig, no matter how small the number of bacilli introduced, is always a fatal disease and is not comparable to the common type of reinfection tuberculosis in man. It is comparable to the malignant primary human tuberculosis, in which sterilization of lesions never occurs. However, in guinea pigs too, a latent form of tuberculosis can be induced by injecting very attenuated germs, and in the disease thus produced sterilization of lesions and loss of tuberculin sensitivity can be observed. Objections can be raised to such a technique. But

in the experimental reproduction of the human type of reinfection tuberculosis not the virulence of the germ is important but the relation between the virulence and the resistance of the body. The resistance of the guinea pig to tuberculosis is obviously too slight to cope with the normally virulent type of tubercle bacillus, but by reducing this virulence it is possible to induce a relation such as exists in man and it is possible to create a condition more closely resembling the human reinfection type of tuberculosis. After injecting a guinea pig with 1 mg. of BCG the tuberculin sensitivity thus produced in the animal only rarely persists for more than ten months. Similarly, tuberculin sensitivity induced by any other attenuated strain disappears after some time. The persistence of such sensitivity depends upon the constitution of the animal. There is a long interval between the sterilization of lesions that had become latent and the moment when tuberculin sensitivity disappears. Experiments have shown that, whereas lesions may become sterile after three months, the tuberculin reaction remains positive for twelve and more months. Thus the substratum of a tuberculin reaction may be something other than living tubercle bacilli. A new infection, following spontaneous loss of tuberculin sensitivity, produces new tuberculin sensitivity, which sets in much more promptly and testifies to the fact that, whereas cutaneous allergy had disappeared, general allergy—that is the ability to react “differently”—had persisted.—*Quelques considérations expérimentales sur les notions de stérilisation des lésions tuberculeuses et d'extinction de la sensibilité tuberculinique récemment étudié chez l'homme*, A. Saenz, *Presse méd.*, November, 1940, No. 93/94, 955.—(G. Simmons)

Chronic Chlorine Poisoning and Tuberculosis.—Groups of guinea pigs were exposed to prolonged inhalations of light concentrations of chlorine before and after infection with tuberculosis. It appears from the results obtained that chronic chlorine poisoning favors the evolution of experimental tuber-

culosis in guinea pigs. Individuals employed in industries where they may be exposed to chlorine fumes should be screened for any evidence of tuberculosis and should be followed clinically and radiologically during the period of employment.—*Action de l'intoxication chronique par une atmosphère de chlore a faible concentration sur la tuberculose expérimentale du cobaye*, F. Arloing, E. Berthet & J. Viallier, *Presse méd.*, April, 1940, No. 33/34, 353.—(G. Simmons)

Precipitin Test for Tuberculin Antibodies.—It has been demonstrated that killed bacteria could be coated with antigen and that such antigen-coated cells made possible the detection of extremely small amounts of antibody; therefore, it was decided to attempt to coat bacteria with tuberculin for the purpose of developing a quantitative precipitin test against tuberculin. *Serratia marcescens* were used because of their small uniform size. The killed cell suspension was diluted so that the nitrogen content was the same as the 0.5 per cent dilution of Old Tuberculin. Equal portions of the dilute cell suspension and 0.5 per cent Old Tuberculin were mixed and incubated at 37.5°C. for twelve hours. The Old Tuberculin was adsorbed on the cells in this interval. The mixture was then centrifuged and the coated cells were washed twice with saline to remove any excess or free Old Tuberculin. The coated cells were finally suspended in physiological saline (pH 6) to a density equivalent to a reading of 70 on the Klett-Summerson photoelectric colorimeter, using a green filter (540 mμ). This suspension was used as the antigen for the test. Five-tenths cc. of antigen was added to serial dilutions of serum ranging from 1:8 to 1:2,048; the tubes were shaken vigorously for five minutes and incubated at 37.5°C. for two hours. The test was read at this time, then placed in a refrigerator at 8°C. for twelve hours, and reread after being allowed to warm up to room temperature. Positive tests were manifested by a fine granular precipitate, best read against a blue light in a darkened room. Two control tubes, namely,

coated cells and saline, and uncoated cells and serum should always be included for each test. It is imperative that the following precautions be observed: (1) Antigen, serum, and saline must be sterile. (2) Antigen, that is, coated cells, must be prepared daily or be kept frozen in a deep-freeze refrigerator at -20°C. (3) The test must not be left in the refrigerator for more than twenty-four hours or false positive tests will result. (4) The precipitate is extremely fine and requires great care and considerable skill for accurate reading. The results obtained with the sera of 12 tuberculous guinea pigs were as follows: 10 developed antibodies but the titers varied from 1:2 to 1:128, one animal failed to develop antibodies and one animal died during the first week of the experiment. The sera of 8 tuberculin-positive and 8 tuberculin-negative patients were tested. One tuberculin-negative individual had antibodies in serum with a titer of 1:128, while all of the tuberculin-positive individuals had positive tests with titers ranging from 1:16 to 1:64. Thirteen sera from patients with active tuberculosis had titers ranging from 1:64 to 1:1,024 and twelve sera from patients with arrested tuberculosis had titers ranging from 1:32 to 1:256. The results obtained suggest that the antibody titer is significantly different in active and inactive tuberculosis and that individuals who do not react to Old Tuberculin by skin test will not have antibodies in the serum. This study is of a preliminary nature, but seems to be of sufficient constancy and interest to justify its presentation.—*Precipitin Test for Tuberculin Antibodies*, R. O. Muether & W. C. MacDonald, *J. Lab. & Clin. Med.*, May, 1945, 30: 411.—(F. G. Petrik)

Fatty Liver.—Among 35 cases of chronic pulmonary tuberculosis that came to autopsy only 3 showed fatty livers and these patients had been rather stout. In two-thirds of the cases examined there was evidence of a typical inflammatory process without evidence of fatty degeneration. Periportal sclerosis was observed only rarely, but massive proliferation of Kupfer's cells was an almost constant

feature. Fat deposition in the liver cells usually starts at the periphery of the hepatic lobule. In order that fat may be deposited, it is necessary for the body to have sufficient reserves in lipids and glucosides and the endocrine system must be functioning normally. A very important factor in the development of fatty deposits is anoxemia. Fatty degeneration was found in livers of aviators flying at high altitudes and could be induced artificially by exposing experimental animals to an atmosphere poor in oxygen over varying periods of time. In the course of chronic pulmonary tuberculosis there is always anoxemia present which is, if not an essential, at least an important additional factor in the development of fatty liver in individuals having sufficient lipid reserves.—*Considération sur le mécanisme de la stéatose hépatique chez les tuberculeux*, P. Florentin, R. Grandpierre, P. Grognot & J. Royer, *Presse méd.*, November, 1943, No. 43, 630.—(G. Simmons)

Chemistry of Tubercle Bacilli.—The aggressive properties of Koch's bacilli are due to lipid substances, particularly those with fatty chains with an acid radical, which have ramifications in α position. These substances, when injected into a guinea pig previously infected with Koch's bacillus, are able to induce Koch's phenomenon in the animal thus treated and are able to produce allergy and immunity in healthy animals. These substances can be prepared synthetically and they assume an importance in tuberculosis similar to that of certain polysaccharides in pneumococcal infections.—*Orientation nouvelle de chimisme bactérien au cours de la tuberculose: Application pratiques*, J. Paraf & J. Desbordes, *Presse méd.*, June, 1943, No. 11, 163.—(G. Simmons)

Activation of Specific Proteolytic Enzymes.—The influence of short waves on specific proteolytic enzymes first described by Abderhalden and found in the urines of patients

with pulmonary tuberculosis was examined. It was found that these enzymes increase under the action of short waves. It is assumed that short waves cause stimulation of the vagus, which in turn brings about changes in the oxido-reductive mechanisms and determines an increase in the proteolytic enzymes.—*L'attivazione delle proteasi specifiche di difesa: Influenza delle onde corte*, F. Ingrao & A. Valli, *Ann. Ist. Carlo Forlanini*, 1942, 6: 741.—(G. Simmons)

Antibodies in Tuberculosis.—In severe caseous pulmonary tuberculosis it is impossible to get an increase of the skin reaction to injection of tuberculin, whereas in productive fibrous processes repeated skin tests revealed an increase of the skin sensitivity to tuberculin. There is a relationship between the reticulo-endothelial system and skin sensitivity, because in those cases in which, following injection of Congo red, the dye was absorbed readily the skin sensitivity was greater than in those in which the reticulo-endothelial system was paralyzed (decreased retention of dye). An increase of the antibodies can be obtained after a specific stimuli, such as exposure of the spleen to X-rays. This was proved by means of passive transmission of antibodies in the blood; 171 experiments of passive transmission were made with 65 blood sera. If the serum was obtained from a person who had a tuberculin injection twenty-four hours before, in 72.5 per cent of the recipients the skin sensitivity to tuberculin increased. With serum obtained twenty-four hours after irradiation of the spleen the skin sensitivity of 87.5 per cent of the recipients increased. In the control series (serum from not treated tuberculous patients) passive transmission was obtained in only 28 per cent.—*Ueber die Rolle humoraler Antikörper in der Tuberkulose allergie*, J. Alfoeldy, *Ztschr. f. Tuberk.*, 1942, 89: 52.—(G. Simmons)

SILICOSIS¹

A Clinical Study

HOWARD DAYMAN

This study deals with the clinical observation of 116 patients with silicosis, 33 of whom came to necropsy. Of the 116 patients, 64 were treated at the Sanatorium for periods averaging seven months, and the remaining 52 were examined in the Out-patient Department. For the entire series, the duration under medical observation averaged three years per patient, with a maximum of sixteen years.

The histories showed that foreign-born laborers from Italy and the Baltic States comprised the greater number of cases. The youngest patient was 31 years of age and the oldest 69, with the majority between the ages of 40 and 55. With few exceptions, previous health had been good. In one instance, pulmonary tuberculosis probably preceded the development of silicosis and in 9 there was a history of pneumonia. Table 1 presents the occupations and periods of exposure to silica dust. In most occupations the average duration of exposure was about twenty years, the longest being forty-eight years for a sandstone worker, the shortest two years for a grinder. A history of prolonged exposure to silica dust was regarded as essential and, in conjunction with the clinical, roentgenological and laboratory findings, formed a basis for the diagnosis of silicosis.

Clinical groups: Of the 116 patients, 30 presented no evidence of clinical tuberculosis and may be conveniently divided into two groups: those with simple nodular silicosis (15 cases) and those with simple conglomerate silicosis (15 cases). Seventy-seven patients with complicating manifest tuberculosis comprise a third group, and lastly there were 9 cases which remained unclassified through inadequate information or because they did not clearly fall in one particular group. Patients who exhibited merely exaggeration of the linear markings on the chest roentgenogram were not included in the present study unless the diagnosis was confirmed at necropsy, since at that stage (often alluded to as the first stage in silicosis) the clinical diagnosis is at times in doubt.

SIMPLE NODULAR SILICOSIS

The majority of the 15 patients in this group were free of symptoms and the condition was discovered on routine examination or because the patient sought advice for some intercurrent ailment. A few noted slight dyspnea on exercise. The diagnosis was established solely on a history of prolonged exposure to silica dust and the minute, widely distributed shadows (2 to 5 mm. in diameter) cast on the roentgenogram. Tubercle bacilli could not be demonstrated in the sputum.

In the absence of complicating tuberculous disease, the clinical course in nodu-

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lar silicosis is in most instances benign, a point previously emphasized by other observers. Among the patients in this group, 4 have died of causes unrelated to silicosis. The remaining 11 have been under medical observation for periods averaging six years, with a maximum of eleven years. During this time, the patients have been able to work, and no material change in the pulmonary condition has occurred. The following case is typical of this group:

Case 1: R. H., age 54, was a magnetite miner for thirty years. The numerous minute shadows on the roentgenogram are the only evidence of silicosis aside from the history. The patient's condition has not changed during nine years of observation. (Figure 1.)

TABLE 1
Occupations and duration of exposure to silica dust

*OCCUPATIONS	CASES	PER CENT	YEARS EXPOSURE		
			Maximum	Average	Minimum
Iron miners.....	72	62	44	21	5
Stone workers.....	22	19	48	21	5
Millers.....	10	9	21	10	2
Coal miners.....	6	5	28	19	8
Foundrymen.....	4	3	33	22	12
Sand blasters.....	2	2	21	19	17
	116	100	48	20	2

* Listed according to the occupation in which they engaged for the longest period.

SIMPLE CONGLOMERATE SILICOSIS

Included in this group are 15 patients with conglomerate silicosis and no tuberculosis so far as could be determined.

The occupational histories are of interest since, on the average, these patients had sustained less total exposure to silica dust than had other patients in the series and were more often additionally exposed to carbon dust. Thus, 7 of the 15 had each worked in dusty trades for less than ten years, and with 3 others the concentration of silica dust in the atmosphere was probably low. In the entire series of 116 patients, 12 had at one time or another been coal miners or had processed graphite, and 7 of the 12 fell in the small group having conglomerate silicosis without manifest tuberculosis.

Patients with this form of silicosis exhibited in varying degree the symptoms and physical signs of pulmonary emphysema. Dyspnea, the initial and cardinal symptom, was often the sole outstanding complaint over a period of years, while those symptoms commonly associated with tuberculosis, such as fever, pronounced weight loss, productive cough, hemoptysis and pleural pain, were absent or inconspicuous in most instances. Salient physical signs were the emphysematous thorax and diminished intensity of the vesicular breath sounds. Expulsion of the reserve air was accomplished with difficulty and evoked widely distributed rhonchi. The vital capacity was often considerably reduced.

In striking contrast to the clinical picture of emphysema, the chest roentgenograms presented evidence of advanced pulmonary disease. In 7 of the 15 cases, massive shadows were situated symmetrically in either lung field at the level of the hila, while in 8 cases the principal shadows were somewhat smaller, more numerous and irregularly distributed. In 12, there were additional minute disseminated shadows compatible with silicotic nodulation, but in 3 cases evidence of discrete nodulation was indefinite or absent. In the majority of instances the low position of the diaphragm and areas of radiolucence, particularly at the bases, indicated the presence of complicating emphysema. In the present group, the shadows on the roentgenogram remained unchanged over long periods. It may be pointed out that neither the discrete nodules nor the conglomerate lesions cast characteristic shadows on the roentgenogram and one may be unable to distinguish between silicosis and neoplastic or infectious disease by X-ray examination alone.

Tubercle bacilli could not be demonstrated in the sputum by microscopic methods supplemented in 8 of the 15 cases by guinea pig inoculation or culture.

The disease in this form ran a protracted course, with gradually increasing dyspnea. Among the 15 patients, 8 have died, 2 of undetermined cause and 2 of causes unrelated to silicosis. The remaining 4 of the 8 deaths were due to complicating pulmonary heart disease with cardiac failure, and occurred four to fifteen years after the onset of symptoms. The 7 surviving members of the group have been under observation for an average of six years and are able to do light work though they are partially disabled by dyspnea. One patient has experienced dyspnea attributable to silicosis for twenty-eight years without becoming unfit for work requiring moderate physical exertion.

Three cases of conglomerate silicosis without clinical tuberculosis came to necropsy. In each instance histological evidence of tuberculosis was likewise lacking. The pathogenesis of these lesions is not clearly understood. They were formerly thought to be a manifestation of simple silicosis. However, nonsiliceous constituents of the dust may have some influence. That of carbon has already been alluded to and other dusts may have a similar action. There is evidence to suggest that the action of an infectious agent, the tubercle bacillus, is additionally required and that in these cases histological as well as bacteriological evidence of tuberculosis has become obliterated. In the lungs of experimental animals, when infection by the tubercle bacillus (*R.*) precedes the inhalation of silica dust, massive fibrosis develops while tuberculosis tends to become obscured (1). Furthermore, in clinical silicosis complicated by obvious tuberculosis, one may frequently trace, by means of X-ray, the appearance and growth of large lesions which at necropsy prove to be made up of silicotic nodules bound in a matrix of hyaline fibrous tissue, typical conglomerate lesions. Such lesions usually show well defined tuberculosis as well, but at times tuberculosis cannot be demonstrated in some of the lesions or in portions of them. In 2 cases of this series, tuberculosis, known to be present during life, could not be identified histologically but virulent tubercle bacilli were present in the tissues. In another instance a clinical diagnosis of simple conglomerate silicosis appeared

to be verified by the absence of tubercle bacilli in the sputum and the failure of the patient to react to the intracutaneous injection of 10 mg. of Old Tuberculin. At necropsy the conglomerate silicotic lesions of the lung and of the mediastinal and paraaortic lymph nodes contained what appeared to be typical tubercles, but there was no caseation and tubercle bacilli could not be demonstrated either microscopically or by the inoculation of susceptible animals. In some respects the findings resembled those of Boeck's sarcoid. It may be stated, therefore, that the combined influence of silica, the tubercle bacillus and, at times, other dusts can bring about massive fibrosis of the lungs while tuberculosis in its turn may become so altered that its identification is difficult.

It has become a common practice to regard all silicosis with massive lesions as "silicosis with infection." It is apparent, however, that in some cases tuberculosis, if present, is entirely latent or healed and plays no demonstrable part in the clinical course. For practical purposes this form of the disease must be considered separately and pending a clearer understanding of the pathogenesis it has been designated simple conglomerate silicosis in this study.

The following cases illustrate the important aspects of this form of the disease:

Case 2: B. D., age 46, was referred to us in August, 1937 because of mild intercurrent ailment. The patient had been a driller in zinc and magnetite mines for approximately nine years. He had suffered no serious illnesses except for a brief attack of pneumonia at the age of 35, from which he made an uneventful recovery. The general health was good. There was mild dyspnea on exercise and evidence of slight emphysema. Examination of the sputum failed to reveal tubercle bacilli. The chest roentgenogram (figure 2) presented massive abnormal shadows in the upper portion of both lung fields with additional minute shadows below. Our diagnosis was nodular and conglomerate silicosis with no evidence of clinical tuberculosis.

Seven years later the roentgenological shadows were somewhat larger and more dense but otherwise the condition had not materially changed. The patient had engaged in light manual work during the entire period.

This history illustrates the benign course pursued by some cases of conglomerate silicosis and emphasizes the importance of complete clinical and laboratory examination. Despite the advanced disease indicated by the roentgenogram, there was relatively little disturbance of pulmonary function and tuberculosis of clinical proportions was not evident. In our experience such patients may often continue gainful employment providing the work is not arduous and they remain under medical supervision. Further dust exposure should, of course, be avoided.

Case 3: J. P., age 49, came to us in June, 1937. The patient had been a magnetite miner for twenty-seven years in a mine where the silica content of the dust was only 10 per cent, and enjoyed good general health until 1936 when he developed dyspnea and cough productive of mucoid expectoration.

The salient clinical findings were those of emphysema. There were no physical signs of cardiac disease. Tubercle bacilli could not be demonstrated in the sputum. The chest roentgenogram (figure 3a) presented massive abnormal shadows in the upper portion of both lung fields with adjacent smaller shadows. The cardiac silhouette indicated beginning enlargement of the outlet of the right ventricle.

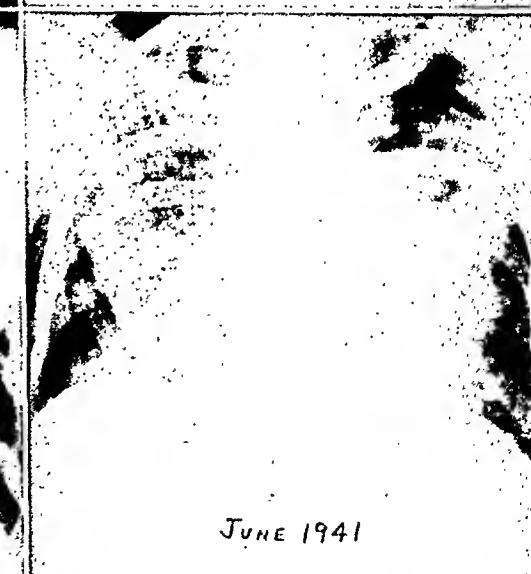
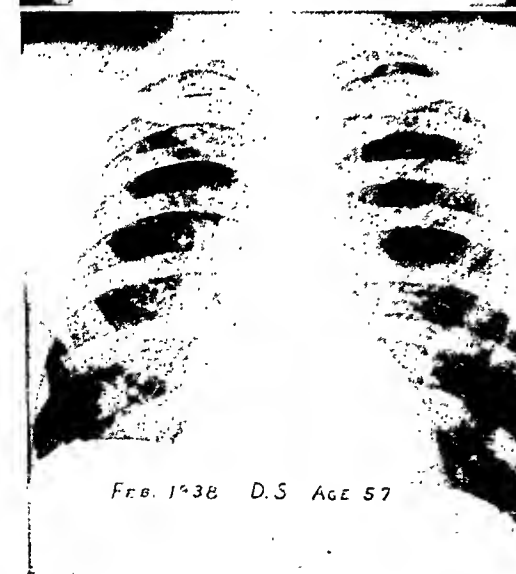
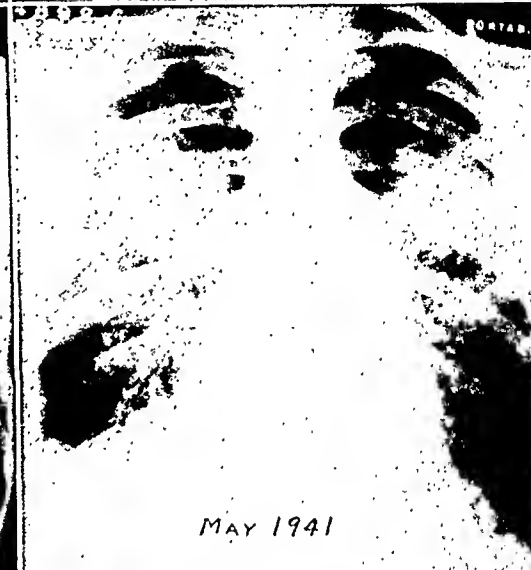


FIG. 1. Upper left; FIG. 2. Upper right; FIG. 3a. Centre left; FIG. 3b. Centre right;
FIG. 4a. Lower left; FIG. 4b. Lower right.

The patient's condition remained unchanged until December, 1939 when he experienced the first of several attacks characterized by the presence of low grade fever, increased dyspnea, clinical and roentgenological evidence of new disease at one or the other lung base, cumulative cardiac enlargement and peripheral signs of cardiac decompensation. At such times the sputum contained black pigment which the patient volunteered was "mine dust." The electrocardiogram traced the development of pronounced right ventricular hypertrophy. The patient succumbed during an attack in May, 1941, five years after the onset of outspoken symptoms (figure 3b).

Autopsy: On opening the thorax, at necropsy, the lungs were emphysematous. In the upper portion of either lung was an area of conglomerate silicotic fibrosis, each containing an antrum approximately 4 cm. in diameter, the lumen partially filled with semi-liquid black necrotic material. The walls presented no pyogenic membrane or other evidence of infectious disease, ulceration being the result of ischemic necrosis. The remainder of the lungs showed small pigmented foci, the majority of which proved to be made up of cellular connective tissue and dust pigment. A few well-formed, discrete silicotic nodules were encountered. There was no evidence of tuberculosis or of passive congestion of the lungs.

Obliterating endarteritis was a conspicuous finding throughout the lungs. Many of the smaller arterics were thrombosed and a few were recanalized indicating that the process had been going on for some time. The artery to the left upper lobe contained a thrombus which had begun peripherally near the area of conglomerate fibrosis and had grown in a retrograde manner until it had occluded a major branch. Arterial occlusion was probably responsible for the recurrent attacks of fever and cardiac failure.

The heart was considerably enlarged due to hypertrophy and dilatation of the right ventricle, the wall of which measured 10 mm. in thickness. That of the left ventricle measured 16 mm. in thickness. The liver showed advanced chronic passive congestion.

In this instance, as in all cases of this type which we have observed, it was impossible to determine from the history how long conglomerate silicosis had been present since its development was not attended by symptoms. Disability was due to emphysema and to pulmonary vascular complications. The latter were unusually pronounced in this patient.

TUBERCULOSIS

Seventy-seven patients came to us with silicosis complicated by clinical tuberculosis.

Though modified by the presence of silicosis, the symptoms were predominantly those of the tuberculous disease and included, in order of frequency, cough, expectoration, dyspnea, weight loss, fever, pleural pain and hemoptysis.

Dyspnea was a variable symptom. It has already been pointed out that, as a rule, simple nodular silicosis caused little respiratory embarrassment, and complicating tuberculous disease of strictly limited extent did not appear to aggravate it appreciably. Dyspnea was constant and severe, however, in those with advanced silico-tuberculous disease or with marked emphysema.

On physical examination, the general condition of the patient was, at times, surprisingly good. We have repeatedly observed, as have others, that the constitutional reaction is not so pronounced when tuberculosis complicates silicosis

as when tuberculosis alone is present. Latent râles were elicited over the upper portion of the lungs in 58 (75 per cent) of the 77 patients, in most of whom, it should be noted, the tuberculous disease was advanced. When present in that location, râles appear to constitute a reliable sign of tuberculosis. Although curving of the fingernails was observed in other forms of silicosis, marked clubbing of the fingers was associated with complicating tuberculosis and occurred in 14 of the 77 patients. Clubbing bore no relationship to pulmonary heart disease.

The chest roentgenogram presented wide-spread minute shadows similar to those observed in simple nodular silicosis together with larger mottled shadows, the latter usually being due to the intimately combined lesions of silicosis and tuberculosis. In 11 of 12 instances where it was possible to determine the initial location of the larger shadows the site of predilection was the upper portion of the lung fields, which suggests the tuberculous nature of the underlying lesion. Later extensions to the middle and lower thirds of the lungs usually obscured the early tendency to involve the upper portion but the summit of the lung frequently became the site of antrum formation.

There was no correlation between the size or number of the silicotic nodules determined roentgenographically and the rapidity with which death from tuberculosis occurred. In 4 cases the roentgenograms presented only the larger mottled shadows when the patient first came under observation and the condition was erroneously ascribed to simple tuberculosis. Minute, widely distributed shadows subsequently appeared in the lower portion of the lung fields, and necropsy in each instance disclosed well defined silicosis as well as tuberculosis. Tuberculosis accelerates the growth and enhances the size of the silicotic nodule and the development of tuberculous disease about the nodule further contributes to a more conspicuous shadow on the roentgenogram. In 3 of the 4 cases tuberculosis pursued a fulminating course.

Tubercle bacilli were demonstrated in the sputum of 65 among the 77 patients. In exceptional cases, despite advanced disease and considerable expectoration, the appearance of tubercle bacilli was delayed for a matter of three to six months, though the organisms were later to be found without difficulty. In the majority of the 12 cases revealing no tubercle bacilli in the sputum, complicating tuberculosis was in an early stage and the patients had been under observation for a relatively brief period.

The infectious complications and their incidence, so far as could be determined in this small series, were the same as in simple pulmonary tuberculosis, with the exception that tuberculous enteritis was relatively uncommon. The complications included: tuberculous pleural effusion—10; intestinal tuberculosis—5; military tuberculosis—5; tuberculous empyema—4; tuberculous laryngitis—4; genito-urinary tuberculosis—3; tuberculous bronchitis—2; tuberculous otitis media—2; cold abscess of the chest wall—1; cold abscess of groin—1.

Barium passed through the intestinal tract somewhat more rapidly than usual in 12 out of 33 cases studied by means of the X-ray, but only 2 showed evidence of tuberculous enteritis, later confirmed at necropsy. Three additional cases at necropsy presented intestinal lesions of minor significance.

The presence of silicosis evidently predisposes the patient to progressive tuberculosis. Sixty-six of the 77 are deceased. Following the development of overt symptoms of tuberculosis or the appearance of acid-fast organisms in the sputum, the average tenure of life was two and one-half years in this series. Of the 11 surviving patients, only 3 have been under observation for more than four years.

Forty-four of the 77 patients were treated at the sanatorium for periods averaging seven months but derived no evident benefit other than transient improvement in general condition. Nevertheless, the need for nursing care and segregation from healthy associates made hospitalization advisable. In 3 instances therapeutic pneumothorax was induced. In each case pulmonary antra failed to close and empyema developed. One patient who was subjected to a thoracoplasty operation after leaving Ray Brook likewise failed to attain an arrest of the disease.

The following cases illustrate this form of the disease:

Case 4: D. S., age 57, had been a mucker in magnetite mines for twenty-seven years. In February, 1938, while apparently in good health, an employment roentgenogram of the chest presented a very few mottled shadows in the right apex and left first interspace and a diagnosis of pulmonary tuberculosis, stage I, was made (figure 4a). The linear markings were exaggerated but evidence of generalized pulmonary fibrosis was so meagre that at first it was thought that the patient did not have an appreciable amount of silicosis.

A few months later, a productive cough developed and on entering Ray Brook in December, 1939 the patient presented the clinical picture of advanced tuberculosis with copious expectoration, dyspnea, low grade fever and emaciation. There were râles over the upper portion of the left lung. The fingers were clubbed. There were no cardiac abnormalities. The chest roentgenogram gave evidence of advanced pulmonary disease with a large antrum in the summit of the left lung. There were numerous minute shadows distributed in all areas not occupied by the larger mottled shadows. The sputum contained numerous tubercle bacilli.

Despite steady progression of the pulmonary disease, the patient's clinical condition showed no great change until May, 1941 when dyspnea became aggravated. In June, 1941 ascites and peripheral edema developed. The roentgen silhouette of the heart became moderately enlarged but details of its shape were obscured by the numerous abnormal shadows of pulmonary origin (figure 4b). There were no cardiac murmurs. The patient succumbed on July 11, 1941, approximately three and a half years after the pulmonary disease was discovered.

Autopsy: Necropsy disclosed the presence of both silicosis and tuberculosis. A large antrum was situated in the upper portion of the left lung, its walls composed of silico-tuberculous tissue with an inner pyogenic membrane. Smaller antra of a similar nature were located in the midportion of the left lung and in the right apex. Numerous gray fibrous nodules, 2 to 7 mm. in diameter, were scattered through the remainder of the lungs. Grossly many of the nodules appeared caseous and microscopically all were found to be involved in the complicating tuberculous process. Interspersed between the nodules were many small caseous tubercles. In the lingual division of the left upper lobe the nodules were aggregated into areas of conglomerate fibrosis. There was no passive congestion of the lungs.

The heart was two and a half times normal size due principally to dilatation of the right auricle and ventricle. The average thickness of the right ventricle was 7 mm., that of the

left ventricle 16 mm. The valves and coronary vessels were natural. There was chronic passive congestion of the liver, ascites, and moderate peripheral edema of the trunk and legs.

This case illustrates the evolution of tuberculosis developing on a background of silicosis. The clinical course is typical of the majority of cases in which the two conditions were associated. It was unusual only in showing meagre evidence of silicosis initially.

Case 5: J. B., age 50, came to us in September, 1940. He had been a magnetite miner for twenty-five years. General health had been excellent until 1937 when cough developed and he gradually became dyspneic. A chest roentgenogram taken in March, 1938 presented evidence of advanced bilateral pulmonary disease. Entering Ray Brook

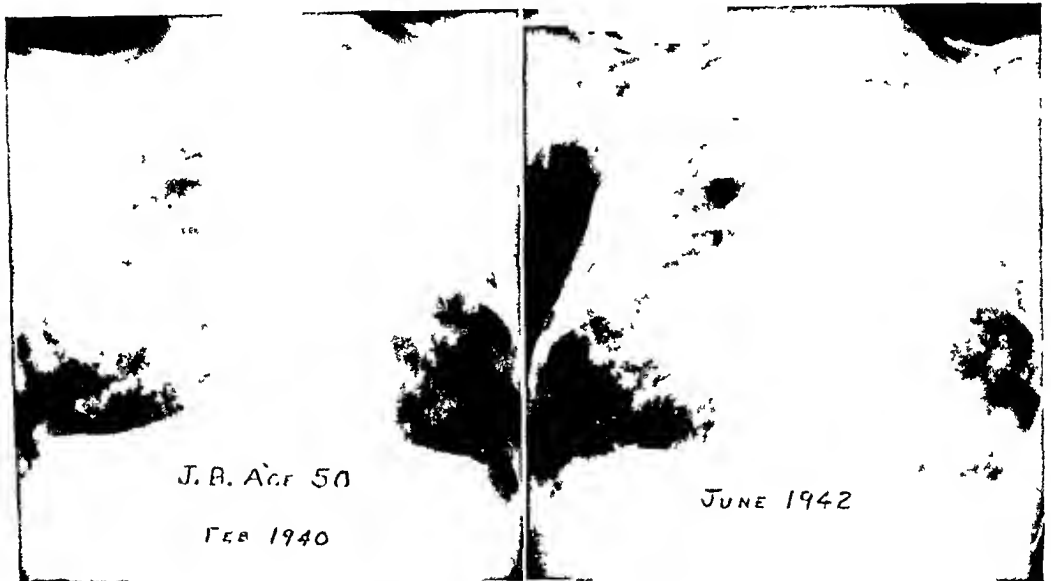


FIG. 5a. Left; FIG. 5b. Right

more than two years later, the patient appeared chronically ill, underweight and was more than moderately dyspneic. The body temperature and pulse rate were normal. Expectoration, though copious, could not at first be shown to contain tubercle bacilli even by numerous cultures and guinea pig inoculations. Physical signs of disease, including râles, were elicited over the upper portion of both lungs. There were no cardiac abnormalities. The fingers were clubbed. Additional findings, probably related to the prolonged action of mineral dust in the atmosphere, were advanced occlusal abrasion of the teeth and pale shrunken lusterless nasal turbinates. The white blood count, differential, and erythrocyte sedimentation rate were compatible with the presence of progressive pulmonary tuberculosis.

The chest roentgenogram of February, 1940 (figure 5a) presented the same appearance as that of March, 1938. There were mottled shadows throughout both lung fields, most numerous at the periphery in the upper portions. Included were a number of dense annular shadows varying from 3 to 15 mm. in diameter, evidence of calcareous shells surrounding lesions both in the lungs and in the hilar lymph nodes.

The patient's clinical condition showed no material change for a considerable period, although several increments of the disease were detected by means of the X-ray (figure 5b). Six months after he entered the hospital, tubercle bacilli were demonstrable in the sputum for the first time. Though few in number at first, they were later found in abundance.

On June 4, 1942 the patient became more dyspneic than usual and deeply cyanotic. The heart was enlarged to percussion and also according to X-ray examination. The patient expired in cardiac failure on June 14, 1942.

Autopsy: Necropsy disclosed massive areas of fibrosis in the upper portion of both lungs and numerous discrete fibrous nodules elsewhere in the pulmonary substance. The tracheobronchial lymph nodes were enlarged and fibrous. Many of the nodes were invested in calcareous shells and similar lesions were found along the ramifications of the bronchi in both lungs. Except for the presence of wide-spread calcification, so far as one could determine both grossly and by microscopic examination, tuberculous disease was restricted to the immediate vicinity of several small cavities and a small area of tuberculous bronchopneumonia, all in the left lung. The conglomerate fibrous lesions contained well formed silicotic nodules. Numerous lymphocytes were observed but evidence of tuberculous disease was lacking except in the above mentioned areas in the left lung. The sole cardiac abnormalities were hypertrophy and dilatation of the right ventricle. The liver showed chronic passive congestion.

In this instance of silicosis complicated by tuberculosis, manifestations of the latter were relatively inconspicuous during life and at necropsy the amount of active tuberculous disease was found to be correspondingly restricted. Such cases comprise a minority among the patients in this series in whom both silicosis and clinical tuberculosis were present. This form of the disease has frequently been described, however, and is apparently common in some industries.

The wide-spread eggshell calcification suggests that at one time all the conglomerate lesions were the site of tuberculous disease, in that respect conforming to the theory that tuberculosis, at least in latent or healed form, was a factor in their development.

PULMONARY HEART DISEASE

Heart disease developing secondary to the pulmonary condition was diagnosed during life or at necropsy in 26 of the 116 cases. Twenty cases of pulmonary heart disease occurred among the 77 patients with silicosis and clinical tuberculosis, 4 occurred in the group of 15 having conglomerate silicosis without clinically manifest tuberculosis, 2 among the 9 unclassified cases and none was found among those with uncomplicated nodular silicosis. The antemortem diagnosis based on the roentgenological evidence of cardiac enlargement and, in most instances, clinical signs of decompensation was made in 16 cases. In each of 13 such cases coming to necropsy the clinical diagnosis was confirmed. A total of 33 post-mortem examinations revealed 10 additional cases of pulmonary heart disease undiagnosed during life.

In the absence of cardiac decompensation, pulmonary heart disease usually escaped detection at the bedside. There were no associated cardiac murmurs and the only suggestive sign was accentuation of the pulmonary second sound.

When cardiac decompensation occurred, as was the case in 14 of the 26 instances, it was manifested by increased venous pressure, enlargement of the liver and dependent edema. Dyspnea became aggravated with the onset of myocardial failure, but orthopnea was not the early and prominent symptom which one observes in cardiac disease primarily affecting the left ventricle. In some cases it was entirely absent. Basal râles when present could be attributed to inflammatory disease of the lungs, an impression borne out at necropsy by the absence of pulmonary edema of cardiac origin. Transudation of liquid into the pleural space was likewise not observed in association with pulmonary heart disease and cardiac failure.

The demonstration of right ventricular enlargement by means of the X-ray was an important sign appearing previous to any definite clinical manifestation of pulmonary heart disease. Preliminary to the taking of roentgenograms, the patient was carefully fluoroscoped with particular attention to the cardiac outline in the right anterior oblique projection; that is to say, with the right anterior surface of the chest against the fluoroscope screen. In this manner, the outlet of the right ventricle was cast in silhouette, permitting recognition of its enlargement which may be lacking in other projections (2).

The electrocardiogram showed right axis deviation in a majority of the cases and aided in the exclusion of myocardial infarction. In one instance, the abnormalities of the electrocardiogram signaled the development of a pulmonary infarct.

Thirty-three of the 116 patients in this series came to necropsy. In the postmortem study of the heart it was necessary to exclude 4 cases because of peripheral hypertension, valvular cardiac disease, myocardial infarction or luetic cardiovascular disease. The findings in the remaining 29 are tabulated below.

<i>Cardiac Abnormalities in Silicosis</i>					
Right Ventricular Changes					
	N	D	H	HD	Totals
N	7	4	3	4	18
		(7-2)			
Left Ventricular Changes	D	2	1	3	6
	H		2		2
	HD			3	3
					} 5
Totals	7	6	6	10	29
			16		

N—normal; D—dilatation; H—hypertrophy; HD—hypertrophy and dilatation.

Hypertrophy of the ventricle wall was considered to be present if it exceeded 5 mm. in thickness on the right or 15 mm. on the left. In a few instances, the presence or absence of hypertrophy was judged by inspection, actual measure-

ment of the wall not having been made. The right ventricle was hypertrophied 16 times and the left ventricle 5 times. In 3 of the 5 cases of bilateral ventricular hypertrophy, the changes on the right distinctly exceeded those on the left.

In 4 of the 6 cases showing cardiac dilatation without thickening of the ventricle walls the dilatation was pronounced and evidence of chronic circulatory failure elsewhere in the body supports the belief that the dilatation was not merely an agonal change. Two specimens presented moderate dilatation of the right ventricle, a finding of questionable significance since there were no other indications of circulatory disease in these instances. In 7 cases the heart appeared normal.

Significant cardiac abnormalities, predominantly those of the right ventricle, were thus encountered in 20 out of 29 necropsies, an incidence of 69 per cent. The nature of the cardiac lesions and the absence of other cardiac or vascular disorder to explain them, led us to conclude that they developed as a result of the pulmonary condition.

Dilatation and hypertrophy of the right ventricle may reasonably be attributed to obliteration of the vascular bed of the lung and hypertension in the pulmonary artery. This may result from obliterative endarteritis or from destruction of pulmonary capillaries attending emphysema. Left ventricular hypertrophy and dilatation is difficult to explain. It should be pointed out, however, that in the experimental emphysema of dogs, Kountz, Alexander and Prinzmetal (3) observed hypertrophy and dilatation of the right ventricle and to a lesser degree hypertrophy of the left ventricle. They also demonstrated bilateral ventricular hypertrophy at necropsy in a large proportion of patients dying with emphysema.

Generally speaking, patients in the present study who for long periods exhibited advanced pulmonary fibrosis with disabling emphysema were more likely to have marked cardiac hypertrophy including that of the left ventricle. Those with nodular silicosis and fulminating tuberculosis as a rule presented less conspicuous cardiac changes. Roessler (2) made a similar observation and concluded that tuberculosis hindered the development of pulmonary heart disease. It appears to us rather that death from tuberculosis took place before advanced cardiac disease could become established.

Although tuberculosis as a complication of silicosis contributes to the development of pulmonary heart disease, tuberculosis by itself seldom causes such conspicuous cardiac abnormality. Among 100 tuberculous men of a similar age group who were treated at Ray Brook, other forms of heart disease were occasionally encountered but none presented the cardiac syndrome observed in the silicotics. Among 77 tuberculous patients, average age 35, coming to necropsy at this Hospital, the incidence of demonstrable right ventricular hypertrophy or dilatation was 12 per cent. Advanced pulmonary heart disease with cardiac failure was observed in a case of extremely long standing fibroid tuberculosis and in one with marked bilateral therapeutic collapse of the lungs but in most instances the cardiac changes were relatively slight.

FRACTURE OF THE RIBS

Fracture of the ribs due to muscular violence occurred in 12 of the 116 patients studied. In each of 8 patients, a single rib was fractured, while in 4 there was involvement of more than one rib. The greatest number of fractures occurring in one patient was five, and the rib most often fractured was the ninth. In no case were the upper four ribs, or the eleventh and twelfth ribs involved. Such fractures occurring in uncomplicated pulmonary tuberculosis are generally situated near the anterior ends of the ribs, but in silicosis the majority occurred in the region of the posterior axillary line. Fracture of the anterior portion of the rib is thought to be due to the antagonistic muscular action of the serratus anterior and the external abdominal oblique (4), but with posteriorly located fractures the mechanism is uncertain. In both cases muscular incoördination during cough would seem to be responsible for the condition, since there is no history of external trauma.

LYMPHATIC SYSTEM

Lymph nodes along the lymphatic channels draining the lungs are invariably enlarged, fibrous and, in the presence of tuberculosis, are tuberculous as well. The parasternal nodes and the nodes adjacent to the aorta, from a point where it enters the abdomen to below the origin of the renal arteries, are similarly involved. Lymph nodes along the free margin of the lesser omentum may also be affected.

The parasternal nodes seldom attain a great size, but one patient, following what was probably a tuberculous pleurisy, developed a tuberculous parasternal abscess in the right second interspace which was incised and drained externally. The underlying lymph node was probably the source of this lesion (5).

In 3 autopsied cases an enlarged silicotic lymph node, lying in juxtaposition to the common bile duct, appeared to have brought about dilatation, and in one instance inflammatory disease, of the biliary tract. One additional patient, three months following a tuberculous pleurisy, developed chronic, asymptomatic obstructive jaundice thought to have arisen through a similar mechanism. Necropsy was not performed in this case.

SUMMARY

This study deals with the clinical observation of 116 patients with silicosis. An attempt is made to correlate the clinical findings with the morbid anatomy through a study of 33 cases that came to necropsy. Pulmonary tuberculosis is the most important immediate cause of disability in silicosis. It is not appreciably influenced by sanatorium treatment or by collapse therapy. Pulmonary heart disease is a frequent complication. The nature of the cardiac lesion and the means of recognizing the condition during life are described. Other complications include: indirect fracture of the ribs, chest wall abscess and obstructions of the biliary tract, the last apparently resulting from extrinsic pressure on the common bile duct by enlarged silico-tuberculous lymph nodes.

SUMARIO

Este estudio versa sobre las observaciones clínicas en 116 enfermos con silicosis; (trata de correlacionar los hallazgos clínicos con la patología por medio de un estudio de 33 casos en que se hizo la autopsia). La tuberculosis pulmonar constituye la causa inmediata más importante de incapacidad en la silicosis, sin que la afectara apreciablemente el tratamiento sanatorial, o la colapsoterapia. La neumonopatía constituye una complicación frecuente. Describense la naturaleza de la lesión cardíaca y los medios de reconocerla durante la vida. Otras complicaciones comprenden: fracturas indirectas de las costilla, absceso de la pared torácica y obstrucción del aparato biliar, debido este último aparentemente a la presión extrínseca que ejercen sobre el conducto biliar los ganglios linfáticos sílico-tuberculosos.

The author wishes to acknowledge his indebtedness to the late Dr. Edward H. Levy who began this study but was unable to continue because of ill health. Dr. Leroy Gardner performed many of the autopsies in these cases. I am indebted to him for his kind advice and for making the facilities of the Saranac Lake Laboratory available to me.

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PONCET'S DISEASE¹

Clinical Observations on Inflammatory and Degenerative Joint Reactions in Tuberculosis

FRANK SELIGSON

Poncet and Leriche in their two publications *Le Rhumatisme Tuberculeux* and *La Tuberculose Inflammatoire* describe numerous extrapulmonary inflammatory and degenerative lesions which in their opinion belong to the clinical picture of tuberculosis. Their observations have been and still are objects of heated argument. While there exists extensive literature on this subject in French, German and Italian, few papers have appeared so far in England and America. The yearly surveys on *The Problem of Rheumatism and Arthritis* by Hench, Bauer, *et al.* in the *Annals of Internal Medicine* devote very little space to tuberculosis as a cause of these conditions, and twice we find a remark by the editor stating that tuberculous rheumatism is not accepted as an entity in the United States.

Lewin in his contribution in Goldberg's *Clinical Tuberculosis* does not mention Poncet's observation at all nor does Rich in his recently published book on *Pathogenesis of Tuberculosis*. Undoubtedly there is great difficulty in defining the limits of the clinical pictures as described by Poncet and Leriche. Their publications give such a wealth of supported and unsupported facts that it is easy to discount all of them if one is not willing to sift the obvious and well-proved ones from those which do not deserve the same credit.

Poncet and Leriche call their clinical entity tuberculous rheumatism, and describe numerous extrapulmonary conditions in the joints and other serous cavities as being caused by the tubercle bacillus. While they mention a wide variety of manifestations, this paper will try to emphasize the occurrence of transitory inflammatory changes in joints and serous cavities of the body as well as the simultaneous or alternating occurrence of degenerative rheumatic arthritic changes in the course of clinical tuberculosis. When Poncet and Leriche published their books, roentgenology played only a minor rôle in the clinic of tuberculosis and this accounts for the fact that they obviously considered many lesions of different origin as tuberculous when full proof could not be given. Nevertheless there remains much of importance in their extensive papers that, even nowadays, gives us important clues as to the pathogenesis of tuberculosis.

Poncet and Leriche do not claim to find in all of their cases the classical proof of tuberculosis, which means the positive guinea pig test on inoculation and the typical pathological-anatomical picture. They maintain that *Le rhumatisme tuberculeux est né de l'observation clinique* and state that, while some of their cases meet the customary clinical requirements for the diagnosis of tuberculosis, very often the circumstantial evidence of clinical factors is considered as satisfactory proof of the tuberculous origin of the arthritic lesion. They admit that in many cases guinea pig inoculation was found negative for tuberculosis and that biopsy

¹ From the Edward Sanatorium, Naperville, Illinois.

showed only nonspecific inflammatory changes. I think that Poncet and Leriche deserve great credit for emphasizing these facts. Their viewpoint has been supported later by pathologists such as Pagel, Huebschmann and Aschoff.

Huebschmann supports the assumption that a *hydrops articulorum* of tuberculous origin really exists in which specific tuberculous changes cannot be found at all—or, if one wants to be more cautious, have not been found yet. Aschoff (quoted from Loewenstein) pointed out in 1921 that a tuberculous infection not only may produce the well known histological picture but *all* forms of inflammation.

The latest and most complete surveys on Poncet's disease were published by Roulet in 1935 and Berger in 1937. Berger, particularly, gives a very elaborate and highly valuable discussion of this debatable but important issue and shows a well balanced judgment regarding the value of clinical observation on one hand and biological experimentation on the other hand. In this country Loewenstein has recently written on tuberculosis and arthritis reaffirming his previous papers. His results, although highly interesting, are being doubted by many observers since he claimed to have found positive cultures of tubercle bacilli from the circulating blood in cases of multiple sclerosis, apoplexy and streptococcus sepsis. Nevertheless, his paper has reopened here the discussion of this problem which deserves so much further investigation.

Poncet and his disciples were of the opinion that bacillary toxins cause the different types of tuberculous rheumatism, the most important of which are:

- 1: Acute or subacute rheumatism of the joints in 20 per cent of tuberculous patients.
- 2: Acute diffuse serositis (15 per cent of acute tuberculous rheumatism).
- 3: Chronic tuberculous rheumatism in its different forms.

The following facts are considered to be proof:

- 1: Coinciding occurrence of polyarthritis and tuberculosis or alternating course.
- 2: Transformation of a "rheumatic arthritis" into a fungous tumor.
- 3: Similar cytology of rheumatic and tuberculous effusions.
- 4: Rheumatic pains follow injection of tuberculin in tuberculous patients.
- 5: Occasionally, a positive guinea pig inoculation from effusion from a joint.
- 6: Some experiments by Courmont and Dor who produced serous arthritis following intravenous injection of attenuated tubercle bacilli.

This opinion is opposed by Buschke who holds that only the presence of tubercle bacilli is certain proof of the tuberculous nature of the lesion. Buschke overlooks the possibility that the residuals of the specific lesions might be non-specific scars.

According to Berger, four ways exist for tuberculous patients to develop an allergic arthritis:

- 1: Bacillary allergic arthritis, with definite pathological-anatomical changes.
- 2: Tuberculin-allergic arthritis.
- 3: Resorptive arthritis.
- 4: Arthritis caused by parallergy (secondary infection).

Whereas the seeding of bacilli does not need mentioning and is generally accepted as valid cause, the existence of diffusible toxins is denied by some authors. However, clinical observation leads to the impression that a toxic-allergic reaction exists. One need only consider the frequent mode of onset of an infraclavicular infiltration! The exacerbation of an infraclavicular infiltrate with pain in all joints resembles almost completely the clinical symptoms of "flu," including even a "sore throat." Many of such cases, first diagnosed as "flu," are revealed later as tuberculous, unfortunately mostly after considerable spread of the tuberculous lesion. It is at this point that this question assumes practical importance.

This view is well supported by Rich who writes: "It is interesting and important that the effects of a marked systematic reaction (fever, malaise, headache, anorexia, joint pains, backache, prostration) are similar to those of anaphylactic 'serum sickness;' they may simulate to a remarkable degree those familiar in influenza."

Galambos, in a very recent paper, emphasizes strongly Poncet's viewpoint which he believes has been substantiated by Loewenstein's experiments.

In his experimental work Klinge created a broad basis supporting the clinical experience. He was able to prove that the same organism could produce septic and purulent inflammation at one time and allergic reactions at other times distant from the original focus of infection. This seems to concur with the clinical experience and there is no reason why the same principle of action could not be expected in tuberculosis. Frequently even repeated guinea pig inoculations from pleural fluid are negative but the consequent clinical course shows the development of tuberculosis. Nevertheless, pleurisy with effusion, the frequent forerunner of parenchymal involvement, is being considered rightly as tuberculous in the majority of cases by most tuberculosis clinicians in spite of negative results of guinea pig inoculations with pleural fluid.

Although a positive guinea pig test proves the presence of a tuberculous lesion, a negative test must be considered with great caution. Sometimes the technique of the investigator is questionable, and it should not be forgotten that our knowledge of the life cycle of the tubercle bacillus is too incomplete to rule out tuberculosis on the basis of a negative guinea pig test. It is a confirmed fact that Boecks sarcoid turns in a considerable percentage of cases into clinical tuberculosis. Nevertheless, prior to this change, bacilli cannot be found by any laboratory method available at this time. This is not meant to belittle the great value of the guinea pig test but should make us reconsider the problem.

Konschegg discusses tuberculous rheumatism and refuses to acknowledge a specific pathological entity on a clinical basis alone. He quotes Ruescher who believes that, due to strong immuno-biological resistance, specific tuberculous changes undergo a fast regression and leave only nonspecific granulation tissue. Such development would also give a satisfactory explanation for the absence of tubercle bacilli; however, Konschegg does not attribute decisive importance to the presence of tubercle bacilli because this would eliminate most cases in spite

of clinical evidence, while presence of tubercle bacilli would be proof of true tuberculous arthritis.

Neumann in his *Clinic of Tuberculosis of Adults* speaks of "beginning tuberculosis hiding behind rheumatism." Out of his vast experience he describes very interesting cases. One of these cases extended over six years and started with pains in the right shoulder and pleurisy. In the course of the following six years deformity of the joints and immobilization of the extremities developed. There was also decreased motility of the spine. Many and extensive attempts with the usual methods of treatment were unsuccessful. Two courses of treatment with Old Tuberculin restored the patient from complete invalidism.

The pulmonary findings in this case were not pronounced but the marked improvement of the arthritis after the change from the usual treatment to tuberculin injections is impressive. Neumann classifies this case according to Bard and Piery as *pleurite a répétition*. He is thoroughly convinced of the tuberculous pathogenesis of many cases of ankylotic deforming arthritis and confirms Poncet's observations with great emphasis.

Fleeting allergic joint reactions can sometimes precede the appearance of a positive skin test. This is described interestingly by Heimbeck who saw swelling of the ankles one month prior to the appearance of a positive skin reaction. One month after the Pirquet reaction had turned positive, a pea-sized infiltrate appeared in the lungs followed at another month interval by a pleurisy with effusion. Heimbeck's case is particularly well observed and he is of the opinion that this is the first description of a rheumatic joint infection prior to pulmonary manifestations.

The underlying anatomical substrate of Poncet and Leriche's "tuberculous rheumatism" is described by Tripier in his *Traité d'anatomie pathologique generale* as follows: "Since we have found in our investigation that the sclerotic diffuse lesions which exist to some extent in all organs are present simultaneously in classical tuberculosis, one has to conclude that they have the same tuberculous etiology as those in which we find the classical changes. The diffuse sclerotic lesion changes without tubercles are probably of tuberculous origin. They are explained by a slow continuous irritative action. . . . In short, one can conceive the problem in the following manner: toxins are secreted by the bacilli somewhere in the organism and enter from there the circulation. They settle in certain joints and produce lesions which do not show the habitual imprint of the bacillus but are nevertheless a definite manifestation of the bacillary toxin. Certain facts support this conception: the arthropathies following a tuberculin injection, the local reactions of rheumatics following a tuberculin test or following an 'ophthalmo-reaction' and the temporal relationship between arthropathies and pulmonary flare-ups."

A little further in the same chapter, he states: "In tuberculous rheumatism as well as in other manifestations of 'inflammatory tuberculosis' the bacillus could be demonstrated only rarely by us as well as by other investigators. Only exceptionally a sample from a joint effusion produces tuberculosis in a guinea pig. If an infection develops it does not begin to appear until long afterwards, perhaps

at the end of two or three months. On the other hand we did not find follicles or giant cells as expression of a specific formation in the synovia. All we could show as evidence was abnormal vascularization and embryonic infiltration with a tendency to organize around the blood vessels. This happens sometimes in the capsules of the joints, in the periarticular and in the connective tissues. Does this suffice to confirm that such a lesion is specific? We do not know it and we can say that in the great majority of the cases of tuberculous rheumatism no specific evolution of the tubercle bacillus could be demonstrated."

In this paper I intend to report several cases which could be classified within the two groups mentioned in the beginning of the paper. The first group shows acute inflammatory and exudative changes within body cavities. The other group will show the occurrence of degenerative arthritic changes during the course of pulmonary tuberculosis. It should be understood that there are also conditions showing both types of lesions.

CASE REPORTS

Case 1: Observed at the New Hampshire State Sanatorium, Glenciff, New Hampshire. R. T., a male patient, age 35, was admitted in January, 1941 with moderately advanced unilateral pulmonary tuberculosis. His sputum was positive prior to admission. Pneumothorax was instituted on the right a few days after admission. On March 18, 1941, he complained of sudden onset of nausea, vertigo and throbbing noises in the left ear. The hearing in the left ear was diminished. The condition was diagnosed as Menière's syndrome. On the next day, the deafness increased and he was still dizzy. Otoscopy showed reddening around the edge of the tympanic membrane. Within the next days the symptoms disappeared gradually. Ten days after the onset of Menière's syndrome the patient showed a sudden swelling of the left knee joint. Fluctuation was felt upon pressure on the patella. The skin temperature was elevated over the swelling. On April 1, 1941 the swelling had disappeared and no pain was felt. A week later only slight dizziness was left.

Epicrisis: The pulmonary findings of this case were of the usual type but the sudden appearance of an effusion in the left knee joint and the ear symptoms were quite unusual. It should be noted that the effusion of the knee joint disappeared within a very few days and that the ear symptoms lasted only about two weeks. It appears logical to assume a common pathogenesis for the joint effusion and the ear conditions. The most probable explanation would be the assumption of a sympathetic effusion on an allergic basis; the short duration lends support to this assumption since there are hardly any other conditions known which could cause similar changes. Recent literature, particularly a paper by Atkinson, suggests strongly that a large percentage of Menière cases have an allergic basis and Atkinson points out that many of them respond favorably to histamine therapy. The transient nature of the joint effusion is of the type described by Poncet and Leriche.

Case 2: Miss M. W., admitted to the Edward Sanatorium April 8, 1944. This patient began to fail in November, 1942 and Addison's disease was diagnosed in December, 1942. She kept on working and was treated with dioxycorticosterone. In December, 1943 she developed a sudden "flu" and a slight swelling of both knee joints was observed. In February, 1944 she was admitted to a Chicago hospital and miliary tuberculosis was found. On admission to the Edward Sanatorium the patient showed the typical picture of Addison's disease and the presence of miliary tuberculosis was confirmed. She continued to

fail during her stay at the Sanatorium and was discharged after six weeks upon the request of her family.

Epicrisis: There is little doubt that hematogenous tuberculosis existed already when Addison's disease was first found. The transient swelling of the knee joints has to be considered either as an allergic manifestation at the time when renewed hematogenous seeding occurred or as a bland spread which was taken care of by a local immunizing reaction. The simultaneous occurrence of rheumatic changes and Addison's disease was already known to Griesinger in 1860. The transient nature of the swelling of the knee joints speaks in favor of an allergic manifestation.

Case 3: H. N., male, 32 years. Admitted to Edward Sanatorium on September 20, 1942. This patient was admitted with a moderately advanced exudative tuberculosis in the left upper lung field with positive sputum. After a short waiting period, pneumothorax was started and a satisfactory collapse was achieved. After two months an effusion formed in the left pleural cavity, which remained serous. In March, 1943, there appeared suddenly an effusion in the left knee joint. An attempt at treating it with local applications did not bring about any noticeable improvement. Simultaneously he developed swelling of several interphalangeal joints. Within the next months he also complained of pain in his right shoulder joint and in the right hip joint. On April 26, 1943, fluid was taken from his right knee joint and sent away for guinea pig inoculation. The result of this inoculation was negative for tuberculosis. During his further stay no noticeable improvement of his joint condition took place and he was discharged to undergo orthopedic treatment. At Wesley Memorial Hospital the synovia of the right knee joint was removed and two specimens examined macro- and microscopically. The findings were:

On October 1, 1943: This specimen consists of three pieces of tissue, one of which appears to be a portion of semilunar cartilage measuring about 3 cm. in length. A small amount of fat tissue is attached. Two smaller pieces of tissue appear to be mostly fat; one is moderately discolored. They measure $\frac{1}{2}$ cm. and $\frac{3}{4}$ cm. in diameter respectively.

Sections of the above mentioned material show numerous fimbriated processes extending from the synovial surface. These are very vascular and infiltrated with lymphocytes, plasma cells, and phagocytic monocytes. Some of these processes are partially covered by cuboidal or flattened epithelium; others appear to be partially exposed. Numerous fibrin masses are also present and are papillary in shape. The synovial membrane is greatly thickened, congested, and edematous. In a very few places there is a hyperplastic thickening of the lining epithelium.

Diagnosis: Chronic papillary synovitis.

On October 18, 1943: This specimen consists of a ragged and thickened piece of synovial membrane, a piece of fat, semilunar cartilage and a strip of skin scar measuring 10 cm. in length. Over the synovial surface of this specimen are a few areas of papillomatous hyperplasia. Injection is moderate. Other areas are smooth. A small amount of fluid contains soft, cream-colored masses in which areas of hemorrhage can be seen.

Sections of the synovial membrane show considerable thickening, with numerous papillary processes projecting from the synovial surface. Lymphoid infiltration is very marked and includes a few follicles. The tissue is very vascular also.

Diagnosis: Chronic polypoid synovitis.

Epicrisis: The clinical course leaves little doubt that pulmonary and extrapulmonary findings in this case are of the same pathogenesis. The extrapulmonary findings showed the tendency to take a prolonged course. The histological examination did not give evidence of what are considered histological findings typical for tuberculosis. It is believed

that his case suggests the ability of the tubercle bacillus to produce nonspecific pathological-anatomical changes. Cases of this type were described by Poncet and Leriche as tuberculous rheumatism. These authors stressed the fact that many of them became chronic and led, over a course of years, to chronic degenerative arthritic changes with slow immobilization of the joints.

Case 4: (Reported from personal communication.) Mrs. M. Sch., a 24 year old intern at the hospital where the author was a resident in 1925. This patient had an infraclavicular right-sided lesion which was arrested after a stay of several months in the Swiss Alps. A few months prior to the diagnosis of pulmonary tuberculosis, she was suddenly taken sick with acute febrile polyarthrititis. She was admitted to the University Clinic at Kiel and treated with salicylates without beneficial results. After several weeks the arthritic swellings disappeared and patient was discharged. A few months later she hemorrhaged and a diagnosis of open pulmonary tuberculosis was made.

Epicrisis: The close sequel of events together with the unsuccessful treatment with salicylates point in this case towards tuberculosis as a common denominator and cause of both conditions. Grocco already considered in 1892 the lack of response to salicylates as a differential-diagnostic means to separate tuberculous and rheumatic polyarthrititis, but this claim has been refuted later on by other authors.

Although nothing is known about a tuberculin test prior to the onset of polyarthrititis, it can be said that this case resembles closely the one reported by Heimbeck which also showed arthritic swellings shortly prior to the appearance of a pulmonary infiltrate.

Case 5: Mrs. R. L., age 56, admitted to Edward Sanatorium on July 11, 1943. This patient had a thyroidectomy in 1921 at the Mayo Clinic and was treated there for thyroid deficiency in 1935. In November, 1940 she noticed a sudden film before her right eye and a hemorrhage in the right vitreous body was found. She was examined at the Mayo Clinic in November, 1940, but no definite statement as to the cause of the hemorrhage was made at that time. Shortly afterwards, she suddenly developed swelling of both knee joints which improved after about three months during which she took Erthron. In 1942 the swelling in both knee joints recurred and lasted through January and February, 1943. This flare-up in the knee joints was followed by a pleuritic effusion on the left. Her attending physician considered her condition as rheumatic and treated her with quinidine because of what he considered a rheumatic mitral lesion with auricular fibrillation. On July 11, 1943 she was admitted to the Edward Sanatorium and had at that time a pleuritic effusion on the right. She reacted positively to the second strength of PPD. An exploratory aspiration was done and the fluid was inoculated into a guinea pig with negative results. The Kahn test was negative. Her X-ray films did not show any parenchymal pulmonary involvement. In December, 1943 she was again examined at the Mayo Clinic following a recurring pleural effusion on the left. At that time evidence of a parenchymal lesion in the lower portion of the right upper lobe was seen and sanatorium treatment suggested. The patient followed this advice and went for a few weeks to the Winfield Sanatorium near Chicago where she was told that her pleurisy was not of tuberculous nature. In March, 1944 she had a short-lasting flu and in October, 1944, she complained again of pleuritic pain in her left side. An X-ray film taken after this was again free of parenchymal lesions.

Epicrisis: Her ophthalmic, pulmonary and arthritic changes should be considered as a nosological entity. Although her pulmonary parenchyma was clear most of the time, eventually a fleeting lesion in the right upper lobe was found at the Mayo Clinic in Decem-

ber, 1943. While one of her attending physicians believed that she had rheumatic heart disease and that her arthritic changes were rheumatic, it is also possible to correlate her heart findings with her thyroid condition which was a very serious one prior to the thyroidectomy. It must be admitted that the bacteriological proof of tuberculosis cannot be given. Her case resembles closely the ones described by Poncet, Loewenstein, Neumann and others. It would be interesting to observe the result of tuberculin treatment on this patient.

Case 6: O. N., male, age 55. Admitted to Edward Sanatorium on January 10, 1944, with bilateral, far advanced open pulmonary tuberculosis. In 1921 the patient had an iritis from which he recovered. His history is not completely clear as to the onset of his pulmonary disease but he reports that he was seen in 1922 by a lung specialist in Vienna and was sent to Meran which is considered in Central Europe essentially a resort place for tuberculous patients. At the same time this lung specialist found a rigid chest cage and in 1927 Bechterew's disease was diagnosed. In 1931 he had a relapse of his iritis and his spine had become completely immobilized. He went again to Meran because he was run down, although he cannot recall cough or expectoration. Prior to his admission to the Edward Sanatorium the patient had been slipping for eighteen months and became acutely ill in December, 1943 due to a bronchopneumonic spread of his old tuberculous lesion. The further clinical course does not add any additional features connected with our topic and may therefore be omitted.

Epicrisis: This patient also shows a triad of ophthalmic, pulmonary and arthritic involvement, and parallels the same train of events as described before. Leading ophthalmologists like Hippel and Meller have frequently emphasized the tuberculous nature of many cases of iritis and proved it by excellent results with tuberculin therapy. It is not a coercion of facts to assume a common pathogenesis for all clinical conditions as they have occurred in this case.

Case 7: W. K., male, 22 years old. This patient was admitted to Edward Sanatorium on April 7, 1943 after routine examination at Northwestern University where he attended Medical School, which he had entered with a negative tuberculin test. Four weeks prior to admission he was suddenly taken sick with an acute pleurisy with effusion which was already receding when he came to the Sanatorium. His X-ray film showed a small amount of fluid in the left costophrenic angle and a small infiltrate above the clavicle. He did not raise any sputum. His tuberculin test now was positive, the sedimentation rate on admission was 23 mm. (Cutler) in one hour. Although the fluid disappeared completely during his stay at the Sanatorium, his sedimentation rate did not change. Three months after admission he complained of slight rheumatic pains in all joints and this was considered clinically at that time as a toxic allergic manifestation of his tuberculosis. An X-ray film taken a week later showed a new small infiltration close to the one seen on admission.

During the further course of the disease his general condition improved greatly but the sedimentation rate did not go down. There was definite regression of both foci and the patient was discharged home after a stay of five and one-half months, to continue his rest.

Epicrisis: The interesting feature of this case is the appearance of a new infiltrate shortly after a temporary attack of rheumatic pain in all joints, and fever. Although this syndrome is not unknown to many tuberculosis specialists, the immediate recheck of the pulmonary condition is frequently omitted and in some cases valuable time is lost. This case matches completely the description given by Rich at the beginning of this paper. However, it has greater importance to the general practitioner who in an overwhelming

majority of cases would consider such a case as "flu" or rheumatism and would not focus his attention on the possible presence of pulmonary involvement without clinical signs, except roentgenological. The result of this fact is that even nowadays 70 to 80 per cent of all sanatorium admissions are far advanced cases which could have been detected much earlier if the symptomatology of beginning tuberculosis were better known. It is the experience of the author that even highly qualified internists are not sufficiently familiar with the acute onset of tuberculous spreads and not infrequently diagnose them as pneumonia in addition to an already existing tuberculosis.

Case 8: Mrs. V. J., 35 years old. This patient was admitted to Edward Sanatorium on March 12, 1944. Three months prior to admission, patient had severe aches all up the spine and across the shoulder blades which were relieved by "many shots of whiskey." However, the aches continued and spread to other joints. Eventually she was hospitalized and a thorough check-up revealed bilateral hematogenous tuberculosis in the upper lung fields and swelling of the hilar lymph nodes. The sputum contained tubercle bacilli. During the month before admission to the Sanatorium, patient had severe pains in the lower part of her legs and there was an erythematous swelling above the ankles. This swelling had the typical appearance of erythema nodosum. The erythema nodosum disappeared within the first two weeks and within four months the pulmonary lesion cleared completely.

Epicrisis: Erythema nodosum has been observed frequently in the course of infectious diseases and Wallgren deserves the credit for describing its frequent occurrence prior and simultaneously to primary tuberculosis. The coincidental occurrence of erythema nodosum with hematogenous tuberculosis in this case leaves little doubt that it must be interpreted as an acute and probably allergic inflammatory manifestation of hematogenous tuberculosis.

SUMMARY AND CONCLUSIONS

The importance of rheumatic manifestations in the course of tuberculosis requires a renewed evaluation. Our present concept of clinical tuberculosis does not take them sufficiently into account and the present bacteriological methods do not seem to support them. Loewenstein and other workers have given some additional weight to Poncet's observations by demonstrating tubercle bacilli in the circulation in various conditions, but his findings have not been generally accepted. However, clinical observations still have their value and cannot be disregarded in view of extensive literature, mostly French and German. More attention should be given to them by general practitioners and specialists. Degenerative arthritic changes as well as transient inflammations are frequent in pulmonary tuberculosis. They often appear suddenly as effusions in various endothelial-lined cavities of the body and also as slowly progressing degenerative lesions in joints. Little has been done as specific treatment, and the use of tuberculin treatment should have a new trial. Prominent authors, such as Neumann in Vienna and others, have proved its value in arthritis and eye conditions which did not show the typical picture of tuberculosis and were considered "rheumatic" by others. Nevertheless they responded well to tuberculin treatment. The knowledge of the clinical picture referred to in this article can be of great help in diagnosing many cases hitherto not recognized as tuberculous, and also can lead

to the detection of many other cases which can be spared a long sanatorium treatment with application of all the modern methods of treatment in the far advanced state of the disease.

Eight cases are reported in this paper, which are believed to support Poncet's and Leriche's observations.

SUMARIO Y CONCLUSIONES

La importancia de las manifestaciones reumáticas durante la evolución de la tuberculosis exige reevaluación, pues nuestro actual concepto de la tuberculosis clínica no las toma suficientemente en cuenta y las actuales técnicas bacteriológicas aparentemente no le prestan apoyo. Loewenstein y otros autores han agregado algún peso más a las observaciones de Poncet al encontrar bacilos tuberculosos en la circulación en varios estados, pero sus hallazgos no han sido aceptados generalmente. Sin embargo, las observaciones clínicas todavía retienen su valor y no pueden desatenderse vista la considerable literatura principalmente, francesa y alemana, que existe, y que reclama mayor atención de parte de los médicos generales y los fisiólogos. Las alteraciones artríticas degenerativas así como las inflamaciones transitorias son frecuentes en la tuberculosis pulmonar, presentándose de repente en forma de derrames en varias cavidades recubiertas de endotelio y también de lesiones degenerativas de evolución lenta en las articulaciones. Poco se ha hecho en cuanto a tratamiento específico, y la tuberculoterapia debería ser objeto de un nuevo ensayo. Autores eminentes, tales como Neumann de Viena y otros, han comprendido el valor de esa terapéutica en los artríticos y los estados oculares que no revelaban el cuadro típico de la tuberculosis y que considerados por otros como "reumáticos", sin embargo, respondieron bien a la tuberculina. El conocimiento del cuadro clínico mencionado en este trabajo puede ser de mucha utilidad para diagnosticar muchos casos no reconocidos hasta ahora como tuberculosos y conducir al descubrimiento de otros muchos a los que puede ahorrárseles un largo tratamiento sanatorial con la aplicación de todos los modernos métodos terapéuticos en el período más avanzado de la enfermedad.

En este trabajo describíense 8 casos que aparentemente apoyan las observaciones de Poncet y Leriche.

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TREATMENT OF PULMONARY TUBERCULOSIS WITH DIASONE¹

KENNETH B. OLSON, JENCE F. THOMPSON AND CLARENCE J. ZINTHEO, JR.

Diasone,² di-sodium formaldehyde sulfoxylate diaminodiphenylsulfone, is said (1) to have been independently and simultaneously synthesized by Raiziss and associates (2), of the Dermatological Research Laboratories, division of Abbott Laboratories, and by Bauer and Rosenthal of the United States Public Health Service. Feldman, Hinshaw and Moses (3) have recently reiterated the opinion that the effectiveness of diasone and promin in experimental tuberculosis may be due to the breakdown of these products to 4,4'-diaminodiphenylsulfone. This latter drug was first synthesized in 1908 by Fromm and Whitman (4). It was first used in 1937 in experimental streptococcal infections in mice but, because of its toxicity and tendency to form methemoglobin, it was discarded in favor of less toxic materials. These drugs are members of the "sulfone" group in distinction to the drugs of the "sulfonamide" group used in other bacterial infections. Several investigators (5, 6, 7) have reported that diasone inhibits the production of tuberculosis in experimental animal, but this inhibition is less marked than that which occurs with either promin or 4,4'-diaminodiphenylsulfone.

Petter and Prenzlau (8) reported a clinical trial with diasone in 44 cases of pulmonary tuberculosis. In their series, 59 per cent of the cases became sputum-negative in from 45 to 125 days, and the majority showed marked clinical improvement while receiving chemotherapy. They stated that 18 per cent of the patients treated were entirely ambulant, so it can be assumed that 82 per cent were receiving some degree of bed-rest which, in minimal or moderately advanced cases over a period of four months, can be expected to exert some beneficial effects.

Any drug which may exert a beneficial influence on pulmonary tuberculosis, and providing the consequences will not be adverse on the host, should be evaluated. It was in such a spirit that the present study was undertaken. The majority of the cases studied were not early exudative cases but the majority did have a large component of exudative disease. The features which were most carefully observed were conversion of sputum, chest roentgenographic findings and closure of cavities. The subjective symptoms and factors such as weight gain, cough and expectoration, were purposely minimized as these factors, while of importance, will vary considerably and inconsistently in a chronic disease such as tuberculosis.

CLINICAL MATERIAL

Ten cases of pulmonary tuberculosis were selected and an attempt was made to match each case with a control case of about the same age and with a similar

¹ From the Firland Sanatorium, City of Seattle Health Department, Richmond Highlands, Washington.

² The diasone used in this work was donated by the Abbott Laboratories to the U. S. Naval Hospital, Seattle, Washington. Captain J. P. Brady of the Seattle Naval Hospital supplied Firland Sanatorium with the diasone used for this experiment.

type of tuberculosis. In establishing a control group, it was thought that some basis for comparison could be established and in such a small series would better serve to evaluate the effectiveness of diasone. All cases were given bed-rest treatment in addition to the diasone or control capsules, for the period of seventeen weeks (119 days). One control case had tuberculous empyema which was occasionally aspirated. Treated cases were given 5 grains of diasone with each meal for a total of 15 grains (1.0 g.) per day. With the exception of 2 instances of severe febrile episodes, the drug was given continuously for seventeen weeks. Control cases were given three similar capsules daily which contained glucose.

Each patient had a roentgenogram of the chest, sedimentation rate, twenty-four-hour sputum concentrate, urinalysis and complete blood count before the start of the experiment. Roentgenograms of the chest and sputum concentrations were repeated every four weeks and the sedimentation rate, urinalysis, blood count and blood diasone level determinations were repeated weekly for five weeks, and then about monthly for the duration of the experiment.

One far advanced terminal case was treated intermittently for four months in addition to the cases mentioned above. It was not felt that diasone influenced the course of this case.

✓ *Diasone determinations:* These were done according to the method described by the Abbott Laboratories (1) and final readings were made with a photo-electric colorimeter as the color reaction was frequently so slight as to make visual readings inaccurate. On one occasion Earl Norris, Ph.D., Professor of Biochemistry at the University of Washington, checked the determinations by spectroscopy and found them within the limits of permissible error. Chart 1 gives a scatter graph of the determinations and shows that it required three to four weeks for the blood level to maintain itself above 1 mg. per cent but the average for most of the period of experiment was between 1 and 2 mg. per cent. It is of interest to note that the highest levels were found in patients who were acutely ill and had fever. In 2 instances high blood level findings seemed to be related with an acute febrile response in these patients.

✓ *Symptoms:* There was no sense of well being, as noted by some observers, which could be attributed to the drug. About 6 patients developed some degree of nausea but this was severe in only 3 patients and gradually disappeared. One patient vomited. These reactions occurred chiefly in the first four weeks of the experiment and gradually disappeared and were never considered severe enough to warrant discontinuing the treatment. It is of interest to note that 2 of the control cases complained of mild nausea. Several of the treated cases complained of nervousness and transient headaches and these symptoms were not as noticeable in the control group. Several patients believed in the earlier period of treatment that cough was reduced and in 2 cases cough was permanently reduced. The remainder of the treated cases did not feel that there had been any permanent change.

✓ *Objective findings:* Eight of the treated cases developed bluish discoloration which is said to be due to development of methemoglobin and sulphhemoglobin in the erythrocytes.

— Avg. Blood Level

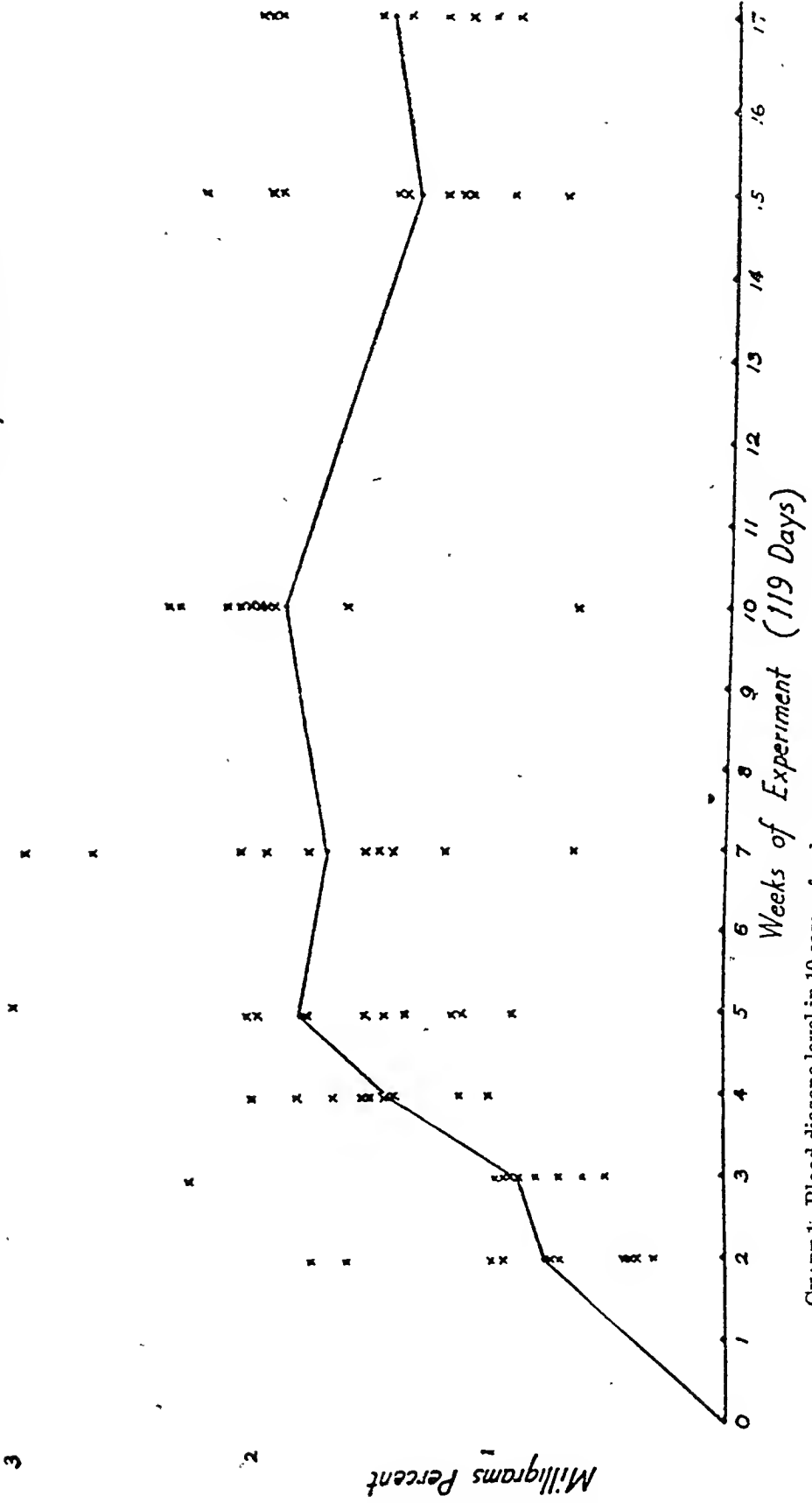


CHART 1. Blood diasone level in 10 cases of pulmonary tuberculosis treated with diasone (1.0 grams per day).

Temperature: Seven treated cases had normal temperature readings at the start of the experiment and 3 patients had fever of over 99.5°F. All but 2 of the patients with normal temperature readings developed slight elevations of temperature of from 0.4 to 0.6 degrees. These elevations tended to decrease toward the end of the experiment. In 2 of the febrile cases the temperature went as high as 103 to 104°F., and in these 2 instances the drug was withdrawn and the temperature promptly subsided. The drug was resumed in both of these cases with no apparent ill effect. One febrile case had progressive elevation of temperature with progression of pulmonary tuberculosis and died shortly following the termination of the experiment. It was felt that the drug had a tendency to cause increased temperature elevation and that this reaction was most marked in acute exudative tuberculosis.

Two control cases were febrile and 8 had normal temperatures at the start of the period of observation. One febrile case developed progressive continued fever to as high as 103°F. One patient with a normal temperature at the start became febrile. One control case became afebrile so that 9 controls had normal temperature curves at the end of the experiment.

Weight: Six treated cases gained an average of three and one-half pounds and 6 control cases gained an average of seven pounds during the four-month period. Four treated cases lost an average of four pounds and 4 controls lost an average of four pounds. There was no significant difference in the treated cases as far as weight gain was concerned.

No significant changes were noted in the urine examinations.

Erythrocyte count: As noted by other observers, there was a sharp reduction in the red cell counts which fell from an average of 4.5 to 3.9 million per cmm. by the fifth weeks. There followed a gradual recovery toward normal. Control cases showed a gradual slight tendency of the red blood cell count to fall.

Hemoglobin: The hemoglobin content of the blood fell quickly after the first week from an average of 13 to a low of 10 g. per cent by the fifth week, and then tended to return towards normal and was above the level of the control group two weeks after termination of the treatment.

Leucocyte count: There was no significant change noted in the white blood cell counts and no case of leukopenia was observed. Differential counts did not show any appreciable change from what was to be expected. Nonfilamented polymorphonuclear leucocytes were increased in those cases with acute disease, as might be expected.

Sedimentation rate: There was a pronounced tendency for the sedimentation rate of all treated cases to decrease. At the start of the experiment the treated cases showed an average sedimentation rate of 13 mm. in one hour, and the controls an average of 16 mm. in one hour. After four months of treatment the average of the treated group was 8 mm. in one hour and the control group showed an average of 15 mm. in one hour. It is difficult to account for this reduction in rate and it is possible that it may be related in some way with the anemia or due to a direct influence of the drug on the blood plasma. This finding warrants further study as it did not necessarily follow the course of the disease as determined by roentgenographic findings.

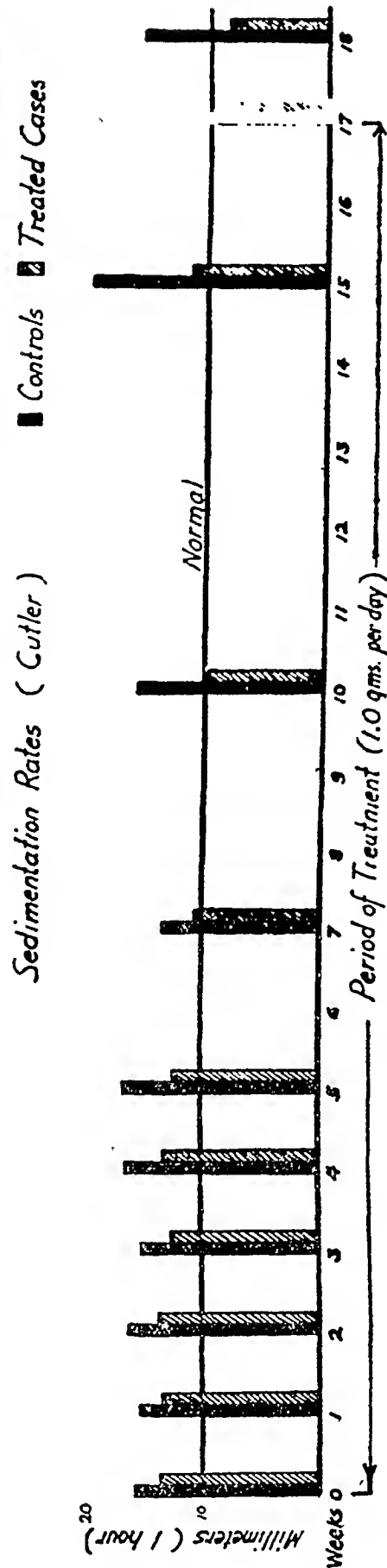
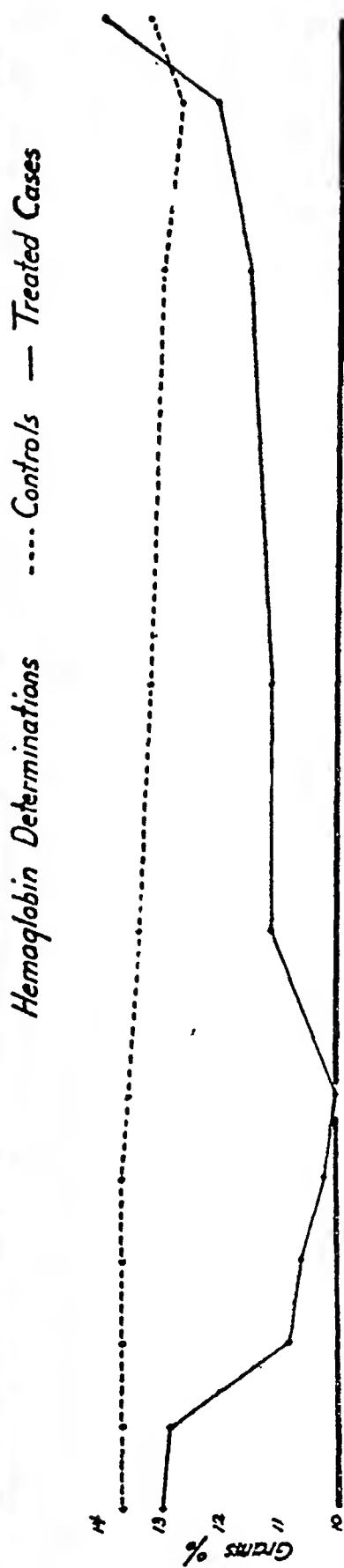
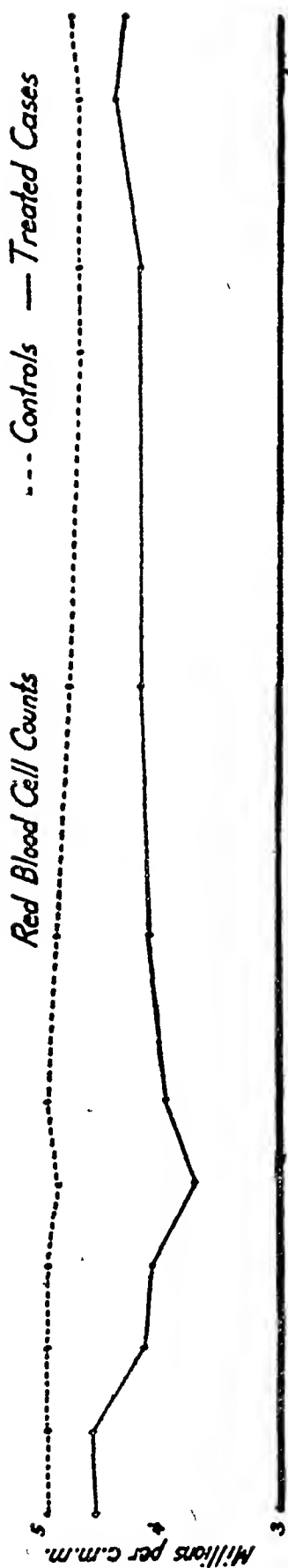


CHART 2. Significant hematological findings in 10 cases of pulmonary tuberculosis treated with diasono.

RESULTS

✓ *Sputum conversion:* Table 1. Seven treated and 7 control cases had positive sputum at the start of the experiment. After four months of treatment 2 treated cases converted their sputum from positive to negative and one treated case had died. Of the control group one case changed from negative to positive but otherwise there was no change. After ten months of treatment and observation, the status of the treated cases was 3 negative, 6 positive and one dead. With the exception of the death, this was the same as at the start of the experiment.

Of the control cases, 5 were negative after ten months and 3 were positive and 2 were dead. There did not seem to be any significant effect on the bacillary

TABLE 1
Results of sputum examinations

	NEGATIVE		POSITIVE	
	Treated	Control	Treated	Control
Start.....	3	3	7	7
After 4 months.....	5	2	5	8
After 10 months*.....	3	5	6 (7)	3 (5)

* 2 control cases and 1 treated case dead.

TABLE 2
Roentgenographic results of treatment

	AFTER FOUR MONTHS		AFTER TEN MONTHS	
	Treated	Control	Treated	Control
Improved.....	4	2	6*	5†
No change.....	2	2	1	2
Worse.....	3	6	2	1
Dead.....	1	0	1	2

* 1 thoracoplasty.

† 2 pneumothorax.

content of the sputum. Results were slightly better at the end of a four-month period of treatment than in the control cases but they were slightly worse in the treated cases after an additional six months' period of observation. It is believed that these are the usual changes which occur in pulmonary tuberculosis and that the changes noted are well within the limits of error.

✓ *Results of chest roentgenographic findings:*³ Table 2 gives a summary of all of the cases treated. After four months 4 of the treated cases were improved, in 2 there was no change noted and in 3 the roentgenograms of the chest showed distinct change for the worse. Of the control cases, 2 were improved, 2 showed no

³ A panel of four physicians trained in tuberculosis work passed on the roentgenographic findings after four months and then after a further six months' follow-up. The physicians did not have advance knowledge as to which were treated and which were control cases.

change and 6 were distinctly worse. At ten months the results in the two series of cases were about comparable.

✓ *Minimal pulmonary tuberculosis:* Only one such case was treated. It was an early exudative lesion and showed gradual improvement during the period of treatment as well as after discharge from the sanatorium. A control case did well also. It is doubtful that diasone influenced the results in this case.

✓ *Moderately advanced pulmonary tuberculosis:* (3 cases) At the end of four months of treatment, 2 cases showed no change and one case revealed definite improvement. During this same period 2 of the control cases became worse and in one there was no change. After an additional six months of observation, 2 of the treated cases showed improvement and in one case there was no change. Of the control cases during this period one was improved, one showed no change and one died from emphysema, pleural effusion and right heart failure (confirmed by autopsy). It seems doubtful that diasone affected this group of cases.

✓ *Far advanced pulmonary tuberculosis:* (6 cases) Three treated cases were worse after four months of treatment, 2 were improved and one case died. The control group revealed 4 cases worse and 2 improved during the same period. The results in this group at four months were about identical. After an additional six months' period of observation, 2 of the treated cases were worse and 3 were improved, one of the latter with a thoracoplasty. The control cases, at ten months, revealed that one case had died, 4 were improved (2 of them with pneumothorax) and one case was worse. All but one of the treated cases showed either exudative or mixed disease and yet few showed improvement. One fibrotic case showed definite improvement which has continued. Two cases with recent exudative disease showed rapid, continued progression despite treatment.

✓ *Cavity closure:* Six treated cases showed roentgenographic evidence of pulmonary cavitation. In one instance a cavity closed while the patient was receiving treatment. Three far advanced control cases had pulmonary cavitation but none closed during the period of observation.

DISCUSSION

The results as shown do not seem to indicate that there was any marked beneficial effect which may have been a result of diasone therapy. Certain effects of diasone, such as the reduction of the sedimentation rate during treatment, may warrant further study. It is entirely possible that diasone may have or produce a systemic response which may inhibit the growth of tubercle bacilli in animals, but as yet there is no proof of its value in human pulmonary tuberculosis.

What can be expected of a chemotherapeutic agent which will control tuberculosis? Zucker *et al.* (9) have set down certain dicta for the evaluation of chemotherapeutic agents in tuberculosis and among others they stress that a trial of one to two months should be sufficient time for a definite beneficial effect to be appreciated. The Abbott Laboratories recommend a minimum period of 120 days for the trial of diasone and from the foregoing material it should be plain that the evaluation of a drug becomes quite hopelessly involved with the natural

evolution of the disease over such an extensive period. Closure of large cavities or resolution of chronic, fibrotic disease by a chemotherapeutic agent seems beyond expectation. The sterilization of the sputum and the rapid resolution of recent exudative lesions and the closure of small cavities all seem within the realm of possibility and these results should be the minimum to be expected from a specific treatment of tuberculosis. On all of these counts, diasone falls quite short of the goal.

Tuberculosis is an infectious process, sometimes acute, more often chronic in character. There is every reason to believe that sooner or later, and it is hoped that it will be sooner, an effective chemotherapeutic agent for the control of tuberculosis will be found. There is as much reason for this hope as there was at one time to hope for a cure of syphilis or osteomyelitis. A specific drug which would sterilize the sputum or even prevent further extension of the disease would be of immense value in the eventual control of tuberculosis. Diasone is not such a drug, although it apparently does exert some inhibitory effect on experimental tuberculosis and is similar to promin in effect.

It is also to be hoped that any agent found will be carefully evaluated, the character and permanence of its effect determined, and its toxicity known, before such discovery is made known to the lay press. Human pulmonary tuberculosis is a vicious disease, but also quite a variable one. The resistance of the host and the character or virulence and number of the invading organisms all influence the type and the ultimate outcome of the infection. Many investigators stress that early, exudative lesions are the type most apt to respond to chemotherapy. These lesions are also most apt to respond to bed-rest or almost any other form of treatment and in many instances will clear without any treatment.

Therefore, it is incumbent upon any investigator to control carefully any apparent results even though the method of control may not be absolutely accurate. It will give a clue as to the efficacy of any new agent.

SUMMARY

1. One minimal, 3 moderately advanced and 6 far advanced patients with pulmonary tuberculosis were treated for a period of 119 days with diasone.
2. There were no significant changes noted in the bacillary content of the sputum.
3. Roentgenographic changes in the lungs were about the same as those observed in a similar group of untreated cases.
4. It is not believed that diasone in the dosage used and under the conditions of the experiment influenced the course of 10 cases of pulmonary tuberculosis beyond what might be expected of bed-rest treatment alone.

SUMARIO

1. Durante un periodo de 119 días se trató con diasona a 10 enfermos de tuberculosis pulmonar: uno mínimo, 3 moderadamente avanzados y 6 muy avanzados.
2. No se notaron alteraciones significativas en el contenido bacilar del esputo.

3. Las alteraciones radiográficas observadas en los pulmones fueron más o menos idénticas a las notadas en un grupo semejante de casos no tratados.

4. Los AA. no creen que la diasona a la dosis utilizada y en las condiciones del experimento afectara la evolución de estos 10 casos de tuberculosis pulmonar más de lo que hubiera podido esperarse con el reposo en cama exclusivamente.

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STRICT BED REST IN PULMONARY TUBERCULOSIS¹

An Appraisal

HARRY A. BRAY

There can be no question that rest in bed is essential in the treatment of pulmonary tuberculosis when manifest symptoms are present. Opinion is divided, however, regarding the practice widely employed in recent years of strict bed-rest for tuberculous patients who are in *good nutrition and free from symptoms or practically so*. Patients on strict bed-rest are enjoined to remain quiet, and bathroom privileges are not permitted. Flat bed-rest is a more rigid form of the treatment, and even the asymptomatic patient at times may not be allowed to feed himself. "To be of benefit, the rest must be complete, mentally and physically. This means flat rest in bed. Even writing, listening to the radio, reading, talking and arguing are activities that may cause an increase in the rate of breathing without your realizing it." (1)

The published results achieved by this form of treatment are few in number; the most important is a study by Amberson (2) of more than one hundred tuberculous patients presenting an "early" lesion. The "early" lesion was located in the upper part of the lung, usually not more than 3 cm. in diameter, and was early in the sense that it was discovered within a year as determined by serial X-ray films. The patients received two to four months of strict bed-rest and a "lasting cure" was obtained in approximately 90 per cent of instances. The measure also apparently prevented the "early" lesion from progressing, since "the majority of early infiltrations developing in young people progress and undergo excavation if not promptly and properly treated" and "most of the untreated cases have progressed into advanced disease." Finally "the experience can be said to approximate closely the results of treatment of minimal lesions reported by Brown from the Trudeau Sanatorium, despite the distinction between minimal lesions and early lesions previously mentioned." There is, insofar as I have been able to determine, no experimental evidence to support the claim that the "early" lesion is especially dangerous. In fact, the studies of Burke (9) with rabbits in sensitized and nonsensitized animals show that the initial lesion in the lung tends to disappear and that after an interval of some months other lesions appear which prove fatal to the animal. The present study tends to confirm the experimental studies of Burke.

In tuberculosis it is agreed that, in general, the more extensive the disease, the less favorable the prognosis. It is surprising, therefore, that the results of treatment at Trudeau were comparable, because minimal lesions are considerably larger than "early" lesions. Moreover, in no instance at Trudeau did the patients receive strict bed-rest; in fact Brown and Heise (3) gave a group of selected patients more rest than was usually prescribed at Trudeau and found that it did not materially affect the progress of the disease. There is apparently

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a marked difference in behavior between the minimal and the "early" lesion in that ample statistical data are available to show that minimal lesions in most instances do not "progress and undergo excavation if not promptly and properly treated" as claimed for the "early" lesion. It would seem therefore that the relatively small "early" lesion is a more dangerous form of the disease, but no pathological evidence on the subject was found after a careful search of the literature. On the other hand, it has been amply confirmed at necropsy that lesions located in the upper part of the lung have a marked tendency to heal.

We have not been impressed by the potential dangers of the "early" lesion from observations made from time to time over a period of years. However, it seemed advisable in view of Amberson's conclusions to make a more careful study of the subject. The present paper deals with a series of 67 patients observed by us who presented an "early" lesion, as described by Amberson, in that it was generally located in the upper portion of the lung and cast a shadow on the X-ray film, soft in appearance, and usually not exceeding an aggregate of 3 cm. in diameter. The disease was less than one year old, and in 23 instances the lesion was six months old or less, as determined by serial X-ray films. In this series of 67 patients there were 27 men and 40 women and the ages ranged between 16 and 54. The average age for the entire group was 23 years. Forty-five of the patients, 17 men and 28 women, were between the ages of 16 and 24 inclusive; the remaining 22 were 25 years old or more. In no instance did the patients receive strict bed-rest; they were ambulant from the time the disease was discovered, throughout their stay at the Sanatorium and subsequently, covering an entire period averaging thirty months. At Ray Brook ambulant patients cure out-of-doors and are on regulated exercise during stated hours of the day. In this group of patients there were not a few who were working up to the time of their admission to the Sanatorium and resumed work shortly after their discharge.

In this series of 67 ambulant patients, the result was favorable in 57 (85 per cent). While slight extensions of the disease were noted at times, particularly during the initial months, these extensions retrogressed, and at the final examination the lesion had remained the same in size, had retrogressed or had resolved, insofar as could be determined by X-ray evidence. Among the 67 patients the result was questionable in 2, and unfavorable in 8 in that the lesion had become appreciably larger. However, it is significant that the disease did not become wide-spread in a single instance during this period of observation averaging thirty months.

The number of patients included in the present study is too small to warrant a definite conclusion, yet the results of treatment here reported in ambulant patients are comparable to those obtained by Amberson by the use of strict bed-rest.

Strict bed-rest is also widely employed in the treatment of incipient or minimal tuberculosis and, in order further to appraise the measure, an additional study was made of a series of 360 patients with incipient disease admitted to Ray Brook during the years 1939 to 1942, inclusive. Under the term incipient or minimal

the lesion may vary considerably in size, which in turn has a direct bearing on the results of treatment. For this reason we subdivided the incipient lesions into three groups: *A* representing a lesion or lesions casting a shadow on the X-ray film the sum total of which is not more than 3 cm. in diameter; *B* somewhat larger; and *C* still larger but conforming to the classification of minimal adopted by the National Tuberculosis Association. In this series of 360 patients where the age of the disease was undetermined, there were 97 who had received strict bed-rest for an average period of four months shortly before admission to the

TABLE 1

Results of treatment of 360 patients with incipient tuberculosis treated at Ray Brook, 1939-1942

	97 PATIENTS WHO HAD RECEIVED STRICT BED-REST		263 PATIENTS WHO HAD NOT RECEIVED STRICT BED-REST	
	Number	Per cent	Number	Per cent
Sex:				
Male.....	60	61.8	120	45.7
Female.....	37	38.2	143	54.4
Extent of lesions:				
A.....	41	42.3	111	42.2
B.....	27	27.8	77	29.3
C.....	29	20.9	75	28.5
Type of shadow:				
Soft.....	82	84.6	246	93.6
Mixed.....	11	11.3	13	4.9
Hard.....	4	4.1	4	1.5
Tubercle bacilli:				
Found.....	45	46.4	111	42.2
Not found.....	52	53.6	152	57.8
Classification on discharge:				
Arrested.....	69	71.1	210	79.8
Apparently arrested.....	12	12.4	31	11.8
Active or quiescent.....	16	16.5	22	8.4

Sanatorium, and 263 who had not received this form of treatment but were ambulant or even working up to the time of their admission. The average age of the patients in both groups was 25 years and the range between 15 and 48 years. In both groups, the nutrition of the patient in general was satisfactory and the symptoms for the most part were mild or absent. The disease, with few exceptions, was located in the upper part of the lung and the appearance of the roentgenographic shadow cast by the lesion (soft, mixed or hard) was comparable in the two groups. Tubercle bacilli were found in the sputum by smear, by the concentration method or by culture in approximately 46 per cent of the patients who had received bed-rest, and in 42 per cent of those who had not

received this treatment. The large majority of the 360 patients in this series were ambulant during their period of treatment at the Sanatorium but in no instance was *strict bed-rest* instituted even in the presence of manifest symptoms. The average period of sanatorium treatment for the two groups was approximately the same—slightly more than seven months.

Table 1 shows that the sex of the patients, the extent of the lesions, and the type of the X-ray shadows were practically the same in the 97 patients who received strict bed-rest previous to admission and in the 263 remaining patients who did not. It is also to be noted that the results of treatment in the two groups are strikingly similar, indicating that, the preliminary months of strict bed-rest did not influence the course of the disease during the period of treatment at Ray Brook.

DISCUSSION

For many years the chief argument for rest in pulmonary tuberculosis has been the success attending immobilization of tuberculous joints. Strict or flat bed-rest (the latter being a more rigid form of the treatment) attempts to immobilize the lung insofar as it is practical to do so. Recently this view has been expressed in literature for the laity. For example: "We cannot put the lung in a splint, but we can reduce its work enormously by rest" (4) and "When one has tuberculosis, whether an early or a more advanced case, the only thing to do is to put one's self in a sling." (5) Yet the indications for and the expected results from immobilization are not the same in the two conditions. For instance, the diseased surfaces of the knee joint are subjected to marked friction and compression. The elimination of these two harmful factors by immobilization explains in large measure the successful results. On the other hand, the pulmonary lesion is not subjected to friction or compression. The only physical agent acting on the lesion is the tension resulting from expansion of the healthy parts of the lung. The degree of tension is usually estimated by the extent of the movement of the lesion. On deep breathing the movement observed fluoroscopically is considerable and some observers believe that the resulting tension is sufficient to produce a loss of integrity of the wall of the tubercle. It is debatable, however, whether the tension increases proportionately with the movement. For instance, the movement of a lesion located in the lower part of the lung is much greater than in the upper, and the extent and direction of its movement at any given point in the lung is modified by the type of breathing, that is, abdominal or thoracic (6, 7). Consequently, the degree of tension exercised on the lesion would vary markedly according to its location in the lung and the type of breathing. Such a view is not supported by valid observations. It seems reasonable to assume that the lesion moves with the lung and that movement *per se* does not indicate the degree of tension on the lesion. Some years ago, Dr. Irving Langmuir discussed with the staff at Ray Brook possible means for determining the degree of tension exercised on the lesion by the expanding lung, but no suitable procedure was found to solve the problem. However, some light was thrown on the subject by experiments conducted by my associate, Dr. Howard Dayman, at Ray Brook. Tuberculous lungs of guinea pigs were ruptured by overinflation either *in situ* or

after removal. It was found that the point of rupture occurred in the healthy parts of the lung, usually distal to the terminal bronchus. There was no evidence of a tear in the wall of the tubercles, all of which were recent and progressive. In view of these experiments, the often expressed opinion that deep breathing may tear the wall of the tubercle is open to question.

In collapse therapy, the contralateral lung not infrequently presents lesions, some smaller, others larger, than the "early" lesion, and they may be less than one year old as determined by serial X-ray films. These recent lesions are subjected to the additional function imposed on the contralateral lung. Yet, notwithstanding, it is agreed that such lesions usually are not activated, but, in fact, often undergo resolution, partial or complete. It is to be noted that these favorable results occur despite the fact that strict or flat bed-rest is generally not instituted in collapse therapy.

The bronchi cannot be immobilized for they are subjected to marked changes in length and calibre incident to respiration. Yet it is well-known that tuberculous lesions of these structures show a definite tendency to heal (8). This observation alone should cast some doubt on the influence of immobilization in the treatment of pulmonary tuberculosis.

There are certain hazards attending the use of strict or flat bedrest for *patients in good nutrition and free from symptoms or practically so*. The enforced curtailment of physical activities is followed by marked loss of muscular tone, disturbance of the physiological processes of the body and accentuation of the fears of the patient consequent to the disease. It is not reasonable to expect that the resistance of the patient to the disease will be fortified at the same time that he is being undermined physically and emotionally. The asymptomatic patient with incipient disease on admission to Ray Brook is under close medical supervision for a period of two weeks; he rests in bed but is allowed bathroom privileges and goes to the dining room for his meals. He then takes the cure on an open porch for several weeks, after which he is placed on graduated exercise out-of-doors for specified periods ranging from five minutes to two hours daily. He is also assigned certain cure tasks which require from five minutes to one hour daily for their completion. Subsequently, opportunity in vocational training is available and represents the final phase in the rehabilitation of the patient. The period of sanatorium treatment for these asymptomatic patients ranges from seven to nine months. If the patient develops manifest symptoms he is placed in bed, but even here the personality of the patient is kept in mind and the measure is not carried to such extremes as to prove harmful.

Trudeau believed that his patients should lead as normal a life as possible within the limitations imposed by their disease, and this has been the guiding principle in the treatment of patients at Trudeau and at Ray Brook since these institutions were founded many years ago.

SUMMARY

There can be no question that rest in bed is essential in the treatment of pulmonary tuberculosis when manifest symptoms are present. Opinion is divided, however, regarding the practice employed in recent years of strict bed-

rest for tuberculous patients who are in good nutrition and free from symptoms or practically so. Patients on strict bed-rest are enjoined to remain quiet, and bathroom privileges are not permitted. Flat bed-rest is a more rigid form of the treatment, and even the asymptomatic patient at times may not be allowed to feed himself. The published results achieved by this form of treatment, however, are few in number and, to my mind, not convincing. A series of 67 ambulant patients was observed by us who presented an "early" lesion—early in the sense that it was less than one year old as determined by serial roentgenograms, and cast a shadow on the X-ray film, soft in appearance and usually not exceeding an aggregate of 3 cm. in diameter. In this series of 67 ambulant patients the results were favorable in 57 instances (85 per cent), questionable in 2 and unfavorable in the remaining 8. Although the number of patients included in this study is too small to warrant a definite conclusion, yet the results of treatment here reported in patients who at no time received strict bed-rest are comparable to those obtained by the use of strict bed-rest.

An additional study was made of 360 patients with incipient disease admitted to Ray Brook during the years 1939 to 1942, inclusive; 97 patients in this group had received approximately four months of strict bed-rest before coming to Ray Brook. The remaining 263 were ambulant previous to and during their residence at the Sanatorium except in a relatively few instances where an exacerbation of the disease occurred subsequent to their admission. The results of treatment in these two groups of patients who received approximately the same period of treatment at Ray Brook were for all practical purposes identical, indicating thereby that the initial months of treatment by strict bed-rest did not appreciably alter the course of the disease.

The physiological processes are disturbed in asymptomatic patients who are treated by strict bed-rest, and there is marked loss of muscular tone. It is not reasonable to expect that the resistance of the patient to disease will be fortified at the same time that he is being undermined physically and emotionally.

SUMARIO

No cabe duda de que el descanso en cama es indispensable en el tratamiento de la tuberculosis pulmonar cuando existen síntomas manifiestos; pero hay discrepancia de opiniones acerca de la costumbre establecida en los últimos años de imponer el encamamiento absoluto a tuberculosos bien nutridos y total o prácticamente asintomáticos. A los enfermos, a los que se le ordena reposo en cama, se les hace permanecer quietos sin permitirles ir al baño. El reposo en decúbito supino constituye una forma más rígida del mismo tratamiento, y a veces no se permite ni al asintomático que se alimenta a sí propio. Sin embargo pocas son las observaciones publicadas acerca de este tratamiento, y al parecer del A. no, resultan convincentes. El A. observó una serie de 67 enfermos ambulantes que presentaban una lesión "temprana": temprana en el sentido de que tenía menos de un año según se determinó con roentgenogramas seriados, y que lanzaban una sombra de aspecto blando en la película y por lo general de no más de 3 cm. de diámetro total. En esta serie de 67 casos ambulantes el resultado fué favorable

en 57 (85%), dudoso en 2 y desfavorable en los otros 8. Aunque ese número de enfermos es insuficiente para justificar conclusiones bien definidas, tratándose de enfermos que jamás habían recibido encamamiento absoluto el resultado es comparable al conseguido con este último.

Hízose otro estudio de 360 casos incipientes recibidos en el Sanatorio Ray Brook de 1939 a 1942 inclusive; 97 de ellos habían recibido unos 4 meses de reposo absoluto antes de ir al sanatorio. Los otros 263 eran ambulantes antes de llegar y durante su permanencia en el Sanatorio, salvo un grupo relativamente pequeño en que se exacerbó la enfermedad después del ingreso. En general fué idéntico el resultado del tratamiento en esos 2 grupos que fueron tratados aproximadamente por el mismo tiempo en el Sanatorio, lo cual indica que los meses iniciales de tratamiento a base de reposo absoluto no afectaron mayor cosa la evolución.

El encamamiento absoluto trastorna los procesos fisiológicos en los enfermos asintomáticos y también acarrea pérdida decidida de la tonicidad muscular. No es lógico esperar que se fortalezca la resistencia del enfermo a la enfermedad si a la vez se le socava física y afectivamente.

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TUBERCULOSIS IN A TROPICAL NAVAL HOSPITAL¹

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The success of the antituberculosis campaign in the United States has contributed greatly to our military strength. One of the serious handicaps of our enemy is the extent of tuberculosis among the Japanese. More Japanese have been killed since Pearl Harbor by the acid-fast bacillus than by all our armed forces. Their death rate from this cause is more than four times that of our own people.

Strenuous efforts have been made to exclude tuberculous persons from entering the Navy. Photofluorographic examinations with 35 mm. films have been ordered for all, and most recent entrants have had the induction examination with the 4 x 5" film, often stereoscopic. Recognizing that some persons had escaped such initial examinations and that others may have become infected or developed clinical disease since, the Navy has ordered an X-ray examination of all personnel who have not had such a film within the past year. Such examination is to be repeated annually on all men under 30 years of age and on all persons at the time of discharge from the service unless such examination has been made during the previous six months.

INCIDENCE OF TUBERCULOSIS IN NAVAL PERSONNEL

Despite efforts made to prevent it by excluding affected recruits, detecting disease as it develops in naval personnel and separating diseased persons from the service as expeditiously as possible, tuberculosis remains a serious source of disease, death and disability. In recent years it has accounted for more than 5 per cent of all deaths from disease and more than 5 per cent of all invaliding from the naval service.

In one hospital in the Southwest Pacific, we have seen more than 50 instances of active pulmonary tuberculosis in five months. Among our patients, this one disease has cost the Navy more men, permanently, than have malaria, dysentery and the venereal diseases combined.

In addition to the 50 cases definitely diagnosed, there were more than twice this number in whom tuberculosis was suspected but in whom the positive diagnosis could not be established with the time and facilities at our disposal. Thus Navy doctors have been looking for tuberculosis, but some of our cases, though far advanced, were recognized only after they had been admitted under some other diagnosis.

¹ The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or as reflecting the views of the Navy Department or the Naval Service at large.

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INFECTION

The majority of our tuberculous patients were under 25 years of age, though the oldest was nearly 40. The value of the tuberculin test in this age group is still inadequately recognized. The tradition of the ubiquity of tuberculous infection dies hard, and the fact that the majority of the young white population have never been infected is not generally appreciated. Recent college freshman examinations in the United States showed that only 18 per cent had positive tuberculin tests.

Tuberculin tests on a group of hospital corpsmen showed only 20 per cent positive, and even on a medical ward with an average age of nearly 30 more than half of the patients were negative. Some of our tuberculous patients reported having had negative tuberculin tests prior to entering the service. In suspects in whom the diagnosis was not confirmed, negative tuberculin tests were useful in ruling out the disease, while positive tests, though not diagnostic, were of value in the interpretation of X-ray films and other data. A wider use of the tuberculin test, in large groups of personnel as well as in individual suspects, is desirable.

Most of these cases of tuberculosis had developed long after the patient had entered the naval service. Only 4 of our cases had been in the Navy for less than a year, and less than a third of them for less than two years. The lower incidence in recent recruits may have been due partly to the more searching examinations recently given, and partly to the time required between infection and detectable disease in those infected after entering the service.

Most of our patients claimed to have felt perfectly well until only a short time before admission. More than a year had generally elapsed after entering the naval service before the first symptoms of tuberculosis were noted. Their health records rarely suggested that they may have had previously diagnosed or suggested clinical disease. Initial X-ray films were almost always negative, and only a few had had any positive X-ray findings previous to the present illness.

EXPOSURE

A family history of exposure to tuberculosis was obtained in half a dozen instances, but in most cases this was too remote to be given much weight, as for example in the 30 year old seaman who had been only two weeks old when his father died of tuberculosis. Exposure to a tuberculous shipmate while in the Navy was reported by an equal number of patients, but it was not always clear whether the shipmate was the source, or one of the victims infected by the present case. That men confined to a naval vessel which carries a crewman suffering from unsuspected active tuberculosis are particularly apt to become infected and develop the disease has been repeatedly observed, both here and elsewhere.

Several instances of tuberculosis in hospital apprentices, pharmacist mates and medical officers point to the special danger for hospital personnel of exposure to the unrecognized open case of tuberculosis, and the need for adequate preventive technique on all hospital admissions until negative tuberculin tests or

X-ray examinations have been obtained. Precautions in the care of known tuberculosis cases should be insisted upon as in all communicable diseases.

CLINICAL FINDINGS

The disease was usually recognized much too late in these men. Most of them had frank and rather characteristic symptoms of consumption in an acute stage, with fever, usually definite though not high, cough, expectoration, loss of weight and weakness. Many also complained of pleurisy or chest pain, hemoptysis, night sweats, excessive fatigability, and occasionally nausea, vomiting, anorexia, headache and frequent "colds."

When these patients were relieved from the strenuous exertions of active naval duty which most of them had been performing up to just before admission, and were put on incomplete rest treatment in our medical wards, the symptoms often promptly ameliorated, though cough and expectoration might not disappear. A few cases were picked up on routine examinations or with the help of incidental X-ray examinations in the absence of any presenting symptoms.

Physical findings were often marked. Impaired percussion note was not noted as often as in the more chronic cases, and breath and voice sounds and vocal fremitus were recorded as abnormal in about half of the cases. Râles, however, especially the posttussic variety, were noted in most of these cases.

Laboratory findings were also generally consistent with the clinical picture. An accelerated sedimentation rate was found in all of the cases with positive sputum. Only simple sputum smears were done, but more than three-fourths of the patients showed acid-fast bacilli. If cultures or animal inoculation of twenty-four hour specimens or gastric lavage were more frequently done, a higher number of positive findings might be anticipated. A moderate leucocytosis was usual, but marked shift to the left or a rise in mononuclear cells was only occasionally noted.

The X-ray findings in these patients were, as usual, more extensive than would be indicated by the history or physical findings. The majority showed widespread ill defined soft densities in the upper and middle lung fields. Infiltration and exudation were common, while fibrosis or destructive lesions with cavitation were uncommon. When cavities were present they were generally ill defined and moth-eaten, though an occasional thin-walled round cavity was seen. Few of these patients showed hilar or parenchymal primary calcification. More often it appeared that the infection had developed before calcification of the primary infection had had time to develop. Some of the lesions may have resulted from progression, perhaps after temporary remission, of the primary lesion itself. The few serial films available for the same patient at relatively short intervals showed a marked lability of the lesions, either as clearing or progression, though this was sometimes exaggerated or concealed by differences in roentgenographic technique.

THE TROPICS

There is a wide-spread impression that tuberculosis is more acute or malignant in the tropics. This idea probably arose from the rapid course and high fatality

of the disease among many native populations of tropical countries. Whatever may be the relative rôle of native susceptibility to tuberculosis among primitive peoples, the infrequency of childhood exposure and the greater virulence of adult infections in such "virgin soil" and the many factors affecting infection and resistance among them, it seems highly doubtful that any meteorological factors are here concerned.

The Eskimos of Alaska and the Lapps of Finland present the same acute and fatal tuberculosis picture seen in the Senegambians from West Africa and the Tahitians of the South Pacific. The toll of tuberculosis among Negroes in northern cities shows that their high rates in Africa and our south are not climatic effects.

From the time of Hippocrates, warm climates have been considered favorable for tuberculosis. The Riviera, Italy and Egypt, California and the great South-western desert have been celebrated as places beneficial for tuberculous patients. Saranac Lake is the outstanding exception and even there the abundant use of blankets, hot pigs and other artificial devices keep the patient warm most of the time. The lessened symptoms and mortality from tuberculosis in the summer-time and the retardation of tuberculosis in experimental animals by warmth indicate that actually the tropics should afford the ideal conditions for recovery from tuberculosis.

Although our hospital is located only a few degrees from the Equator, it is not believed that this has had any effect on the incidence or type of tuberculosis we are seeing. Less than 10 per cent of the natives tested here have shown positive tuberculin reactions and only a few instances of pulmonary tuberculosis have been described among them. One of our own patients reported that his symptoms had developed while he was in the Aleutians, another in France and many while on the high seas.

Repeated exposure to heavy infection, especially in subjects who have not had the benefit of previous small, avirulent or dead immunizing infections, crowding in inadequate living space and lack of sanitary provisions and ventilation, food deficiencies, both quantitative and qualitative, and especially the performance of strenuous physical exertion after the onset of the infection, and stoical disregard for early symptoms would rather seem to be incriminated than the tropical climate.

Tuberculosis is always a dangerous disease. In the Navy it has exceptional significance because of the unavoidable close quarters of existence, the importance of continuous physical fitness and the rich resources available for its control by exclusion, prevention, detection and care. Every effort should be made to take advantage of this opportunity.

SUMMARY

Despite its admirable antituberculosis control program, the Navy still suffers from cases of this disease. Fifty instances in one tropical Naval hospital are analyzed. Most of them are young adults, who apparently had only recently become infected and developed clinical disease. The lesions were chiefly infiltrative and exudative, were highly labile and showed a rapid symptomatic

response to rest treatment. The tropical climate did not appear to present additional hazard to these patients.

SUMARIO

A pesar de su admirable plan de lucha antituberculosa la Marina de Estados Unidos todavía tiene casos de la enfermedad. Analizáanse 50 casos de un hospital naval en los trópicos. La mayoría son jóvenes que aparentemente se han infectado recientemente manifestando enfermedad clínica. Las lesiones fueron principalmente infiltrantes y exudantes, muy lábiles y revelaron una rápida respuesta sintomática al tratamiento del reposo. El clima tropical al parecer no creó nuevos riesgos para estos enfermos.

END RESULTS OF ARTIFICIAL PNEUMOTHORAX¹

A Review of 140 Cases Two Years after Reëxpansion

I. V. ALLEN AND C. W. KELLY

This report includes all of the unilateral cases (128) and bilateral cases (12) discontinued at the Saint John Tuberculosis Hospital during a four-year period, 1939 to 1942 inclusive. No cases in whom pneumothorax was unsuccessfully attempted and no cases in whom pneumothorax was discontinued as ineffective within a three-month period, as suggested by Peters *et al.* (1), are included.

The unilateral and bilateral cases were considered separately, but the criteria for appraisal were the same, namely the standards recommended by Bloch, Tucker and Adams (2): "(1) Restoration of the lung to its physiologic function, i.e., complete reëxpansion; (2) adequate roentgenologic evidence of healing of the tuberculous involvement, especially of the disappearance of cavities; (3) return of the patient to normal life, with (4) persistent absence of tubercle bacilli in the sputum; (5) persistent absence of all symptoms of activity, and (6) complete disappearance of all extrapulmonary complications. *Only after at least two years of satisfactory application of these criteria should a patient be considered as cured by the treatment.*"

All of the cases that fulfilled the above requirements were grouped under "satisfactory" results and the remainder under "unsatisfactory" or "dead."

Studying these results, an attempt was then made to determine what factors influenced the result in each case.

The unilateral cases were classified according to the extent of disease, using the National Tuberculosis Association standards, and the results are shown in table 1.

In the complete series of 128 cases, 72, or 56.3 per cent, are satisfactory, 47, or 36.7 per cent, are unsatisfactory and 9, or 7 per cent, are dead. Of the 9 dead, 6 or 4.7 per cent, died of tuberculosis.

Of the 72 satisfactory cases, 12 required intrapleural pneumonolysis before adequate collapse was obtained, 7 cases had phrenicotomy before or at the time of termination of pneumothorax and 3 had a contralateral thoracoplasty performed for apical cavities which antedated or were present at the time of diagnosis of disease on the side on which pneumothorax was instituted.

Of the 47 unsatisfactory cases, there were 22 cases definitely improved by the treatment, 22 cases unimproved and 3 in whom insufficient information was obtained.

Of the 22 cases improved by pneumothorax therapy, 12 were placed in the unsatisfactory group, due to X-ray evidence only, 4 because of contralateral flares, the original lesion appearing healed two years after reëxpansion, and 6 because of persistent fluid, but all of these had sputum conversion.

¹ From Saint John Tuberculosis Hospital, East Saint John, N. B., Canada.

² Complete reëxpansion, as defined by Bloch in a private communication, is complete reabsorption of air from the pleural cavity and the obliteration of the pleural space.

Of the 22 cases unimproved by pneumothorax therapy, 12 had inadequate collapse due to massive pleural adhesions, and at present our impression is that pneumothorax should have been discontinued sooner and thoracoplasty substituted, at least in those cases having cavity in the upper lung fields. In 1934 Coryllos (3) expressed his opinions on the respective indications for pneumothorax and thoracoplasty with special emphasis on the limitation of pneumothorax therapy as compared to thoracoplasty. We consider his warnings well advised. Of the remaining 10 in the unimproved group, 4 were unhealed after reexpansion, 3 had contralateral cavities, one a contralateral flare and 2 developed tuberculous empyema.

TABLE 1

Results of terminated cases two years after reexpansion of lung

	MINIMAL		MODERATELY ADVANCED		FAR ADVANCED		TOTAL	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
Satisfactory.....	12	75.0	26	53.0	34	54.0	72	56.3
Unsatisfactory.....	4	25.0	20	40.8	23	36.5	47	36.7
Dead.....	0	0.0	3	6.2	6	9.5	9	7.0
Total.....	16	12.5	49	38.3	63	49.2	128	100.0

TABLE 2

Relation of duration of collapse to end results in 128 cases

	UNDER 1 YEAR	1-2 YEARS	2-3 YEARS	3-4 YEARS	4-5 YEARS	OVER 5 YEARS
Satisfactory.....	5	10	11	10	18	18
Unsatisfactory.....	17	8	11	5	2	4
Dead.....	3	1	0	2	1	2

Of the 47 unsatisfactory results, 12 were finally made satisfactory by thoracoplasty, one by thoracoplasty and lobectomy.

A comparison of the duration of pneumothorax therapy with end results was then made, grouping the cases in six time divisions, from under one year to over five years, in table 2.

If all the cases receiving pneumothorax for less than three years are added together and compared with all those receiving pneumothorax for more than three years, a definite variation in results is obtained. In the satisfactory group, 26 cases received pneumothorax less than three years and 46 cases received pneumothorax more than three years. In the unsatisfactory group, 36 cases received pneumothorax less than three years and 11 cases received pneumothorax more than three years. This difference seems significant.

The cases having positive or negative sputum, on direct smear only, before the initial pneumothorax, were listed and it was discovered that, of 83 with positive sputum, 44 were finally satisfactory and 39 unsatisfactory or dead. Of

the 45 patients with negative sputum, 28 were satisfactory and 17 unsatisfactory or dead. As the determination of the presence of tubercle bacilli was made only on direct smear previous to therapy, whereas, at the end of therapy, the usual procedure was to have a six weeks' culture on a seven-day concentrated specimen, the original reports are not on a comparable basis.

A review of the chest roentgenograms showed that, of 68 cases having evidence of cavity, 38 were satisfactory results and 30 unsatisfactory or dead. Of 60 cases showing no evidence of cavity, 34 were satisfactory and 26 unsatisfactory or dead.

All groups received similar strict bed-rest for an average period of at least six months after initiation of pneumothorax and remained in hospital for an average period of slightly more than one year.

All the reports of fluoroscopic examinations before and after refills, and all the roentgenograms were grouped according to the degree of collapse which was usually present on quiet breathing. The degree of collapse was divided into

TABLE 3
Relation of fluid formation during therapy to end results in 128 cases

	NUMBER OF CASES WITH FLUID				NUMBER OF CASES WITHOUT FLUID			
	Minimal	Moderately advanced	Far advanced	Total	Minimal	Moderately advanced	Far advanced	Total
Satisfactory.....	8	10	15	33	4	16	19	39
Unsatisfactory.....	2	8	17	27	2	12	6	20
Dead.....	0	2	1	3	0	1	5	6

less than 50 per cent, 50 per cent and greater than 50 per cent; and it was found that of all the satisfactory cases, 73 per cent had been maintained with a collapse of 50 or more per cent. However, our impression was that the most important factor in collapse was whether the collapse was selective and effective, or contraselective and ineffective, as described by Mason (4).

In an attempt to maintain an effective collapse, the manometric pressure readings varied in different cases from positive to negative, but our usual practice has been to maintain a final mean pressure of slightly less than atmospheric, even though this necessitated more frequent refills.

All the chest roentgenograms for each patient were then reexamined and all the fluoroscopic reports reviewed to discover those cases showing any evidence of fluid at any time. Even those cases showing a small amount of fluid obscuring the costophrenic angle were included. The results are given in table 3.

Of the 128 cases, 46.9 per cent developed clear fluid, 28.3 per cent of these being febrile effusions, and 2.3 per cent developed empyema, giving a total of 63 patients, or 49.2 per cent, having fluid at some time. Although our series is small in number, the number of cases developing empyema compares very favorably with those cases reported by Miller *et al.* (5) and with the reported cases and compiled statistics of Weisman (6).

Of the 2.3 per cent, or 3 cases, which developed empyema, one was a tubercu-

lous empyema occurring in a patient while at bed-rest in hospital and one was a tuberculous empyema occurring in a patient having persistent fluid for two years before returning to hospital. The third case was a staphylococcal empyema which developed while the patient was receiving refills from his private physician. Aycock (7) reports that the hazard of such complications as pleural effusion and spontaneous pneumothorax exists so long as a pneumothorax space is present. From our experience pleural effusion is the most feared complication. A recognized spontaneous pneumothorax did not occur in any case in this series.

The next appraisal was a critical inspection of our judgment to determine whether the cases, that had been terminated because duration of therapy was considered adequate, were satisfactory or unsatisfactory two years after pneumothorax was discontinued. After careful consideration they were finally grouped in table 4 under "Intentional" and "Unintentional," according to Peters *et al.* (1).

"Intentional," 103 cases, included all those in whom the refills were discontinued on our advice. "Unintentional," 25 cases, included 20 in whom the

TABLE 4

Relation of intentional and unintentional termination of collapse to end results in 128 cases

	TERMINATION INTENTIONAL				TERMINATION UNINTENTIONAL			
	Minimal	Moderately advanced	Far advanced	Total	Minimal	Moderately advanced	Far Advanced	Total
Satisfactory.....	8	22	30	60	4	4	4	12
Unsatisfactory.....	3	16	17	36	1	4	6	11
Dead.....	0	1	6	7	0	2	0	2

pneumothorax space was lost due to progressive obliterative pleuritis and 5 in whom pneumothorax was abandoned by the patient.

Referring to table 4, it is noted that, of the 103 cases intentionally terminated, 60 belonged in the satisfactory group, 36 in the unsatisfactory and 7 were dead. Of the 60 in the satisfactory group, 50 were discontinued because the duration of therapy was considered adequate, 3 were discontinued because the collapse had become contraselective, 3 were discontinued after phrenicotomy, 3 because of febrile effusion and one because of staphylococcal empyema, accompanied by parietal and visceral pleuritis.

Of the 36 in the unsatisfactory group, 11 were discontinued because the duration of therapy was considered adequate, 8 because of persistent clear fluid following a febrile effusion, 2 because of tuberculous empyema, 11 because the disease was uncontrolled by pneumothorax and 4 because of contralateral flares.

Of the 11 unsatisfactory cases in whom duration was considered adequate, 5 cases were considered unsatisfactory because of X-ray evidence only. These 5 are well and working and have negative sputum. One case showed a new area of disease two years after reexpansion, during the time when he was undergoing major abdominal surgery. Two cases showed evidence of unhealed disease two

years after reëxpansion. One case has a satisfactory chest X-ray appearance and has had sputum conversion, but has marked fatigue and feels unable to work. One case is reported as well and working, with negative sputum, but has refused to return for chest roentgenograms, and one case had incomplete reëxpansion of the lung following six years of pneumothorax therapy which caused a large cavity to disappear and made him sputum-negative. He had persistent clear fluid with tubercle bacilli present on culture.

Of the 7 in the dead group, 2 were discontinued because duration of therapy was considered adequate, 2 were discontinued because of progressive bilateral disease, 2 because of contralateral flares and one because of a febrile effusion.

Of the 2 dead cases in whom duration was considered adequate, one received pneumothorax for 7.5 years, then developed a contralateral flare and died at home of progressive disease. The other received pneumothorax for five years, the pulmonary lesion appearing healed at the time of his death, from carcinoma of the sigmoid colon.

TABLE 5

Results in 12 bilateral cases two years after reëxpansion

	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED	TOTAL	PER CENT
	Number of cases	Number of cases	Number of cases		
Satisfactory.....	0	1	2	3	25
Unsatisfactory.....	0	4	2	6	50
Dead.....	0	0	3	3	25

Referring again to table 4, it is noted that, of the 25 cases unintentionally terminated, 12 belonged in the satisfactory group, 11 in the unsatisfactory group and 2 were dead.

Of the 12 in the satisfactory group, 2 were discontinued by the patient after two years of collapse therapy and 10 developed obliterative pleuritis after an average duration of collapse therapy of 1.4 years for the group. This duration is much less than would be considered adequate, but produced satisfactory results two years afterwards. This observation with some discussion as to the reasons has already been reported by Eglee and Jones (8).

Of the 11 in the unsatisfactory group, 2 were discontinued by the patient after two years of collapse therapy and 9 developed obliterative pleuritis after an average duration of collapse therapy of 1.2 years for the group.

Of the 2 in the dead group, one was discontinued by the patient after 1.25 years and was later reported as lost at sea due to enemy action. The other case developed obliterative pleuritis and died of coronary thrombosis following a second stage of thoracoplasty.

The 12 bilateral cases were also classified according to the extent of disease, and the results are shown in table 5.

Although the same methods of study were applied to this group the small

number of cases does not justify a detailed report in this paper. All the 12 cases had positive sputum previous to collapse therapy and all cases had strict bed-rest for more than six months after each initial pneumothorax. The satisfactory group were perfectly coöperative throughout and developed no pleural complications. One of these had an intrapleural pneumonolysis for a string adhesion. These 3 cases were under ideal working conditions, while they were receiving simultaneous pneumothorax therapy, being employed on part-time duty and later full-time duty at the hospital.

Of the 6 unsatisfactory cases, one is so categorized on X-ray evidence only and has had a confinement without showing any exacerbation of disease six months later. Another has been salvaged by thoracoplasty, and in critical retrospect we think should preferably have been treated by thoracoplasty or lobectomy when the disease was first discovered to be a unilateral upper lobe tuberculous cavity.

The 3 cases in the dead group all died of tuberculosis, 2 of them suffering severe respiratory distress for many months from a bilateral fibrothorax, which developed after febrile effusions.

CONCLUSIONS

Artificial pneumothorax is one of the established methods used to arrest and sometimes apparently cure this preventable disease.

In order to obtain a good result, the coöperation of the patient is essential; adequate bed-rest is necessary as well as aseptic technique on the part of the operator and close supervision during the entire course of therapy by a specially trained and conscientious physician.

A skilled surgeon to perform intrapleural pneumonolysis, when indicated, should be available.

Pneumothorax should be considered as only one of the available surgical procedures to achieve the final objective which is an apparently cured patient.

The formation of fluid is a serious complication and, if persistent, is an indication for reevaluation of the case and consideration of other surgical means for the control of the disease.

Bilateral pneumothorax is very difficult to maintain satisfactorily.

SUMMARY

A review is presented of the end results two years after reëxpansion in 128 unilateral and 12 bilateral cases of pneumothorax.

Out of the 128 cases, 17 developed febrile effusions, 2 tuberculous empyema and one a staphylococcal empyema.

In the group of 72 satisfactory cases, 12 had intrapleural pneumonolyses, 7 had phrenicotomies and 3 had contralateral thoracoplasties.

In the group of 47 unsatisfactory cases, 12 were apparently cured by thoracoplasty and one by thoracoplasty and lobectomy.

In the series of 128 unilateral cases, 72, or 56.3 per cent, are satisfactory or cured; 47, or 36.7 per cent, are unsatisfactory, although 22, or 17 per cent, were

definitely improved; 9, or 7 per cent, are dead, 6, or 4.7 per cent, having died of tuberculosis.

In the series of 12 bilateral cases, 3, or 25 per cent, are satisfactory or cured; 6, or 50 per cent, are unsatisfactory; 3, or 25 per cent, are dead.

SUMARIO

Preséntase un repaso del resultado terminal a los dos años de reexpandir el neumotórax en 128 casos unilaterales y 12 bilaterales.

De los 128 casos, 17 manifestaron derrames febriles, 2 empiema tuberculoso y uno empiema estafilocócico.

Del grupo de 72 casos satisfactorios, en 12 se habían practicado neumonolisis intrapleural, en 7 frenicotomías y en 3 toracoplastias contralaterales.

Del grupo de 47 casos no satisfactorios, 12 se curaron aparentemente con la toracoplastia y uno con la toracoplastia y la lobectomía.

De la serie de 128 unilaterales, 72 (56.3%) se encuentran en estado satisfactorio o curados; y 47 (36.7%) no satisfactorios, aunque 22 (17%) mejoraron decididamente; 9, (7%) han muerto y 6 (4.7%) han muerto de tuberculosis.

En la serie de 12 casos bilaterales 3 (25%) se encuentran en estado satisfactorio o curados; 6 (50%) no satisfactorio y 3 (25%) han muerto.

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A SUCTION CABINET FOR USE IN CAVITY ASPIRATION (MONALDI)

WARRINER WOODRUFF¹

Probably the most important mechanical factor in the successful treatment of tuberculous cavities by aspiration is a dependable source for providing constant negative pressure at a predetermined level.

The more common sources for securing such pressure are:

- 1: Two water bottles with alternating and varying elevations.
- 2: The water pump.
- 3: A central source of negative pressure with pipes throughout the hospital.
- 4: An electric pump.

We have used all of these but have found the first two unsatisfactory. For several years we have been using an electric pump as the source of suction. With the aid of our cabinet maker, Mr. Robert Purvis, we have devised a fitted cabinet which has proved very satisfactory, a separate cabinet being used for each patient. It is large enough to act as a bedside table (figures 1 and 2).



FIG 1 A photograph of the cabinet at the bedside. Note its height, the location of the switch, and the location of the gauge

¹ Saranac Lake, New York.

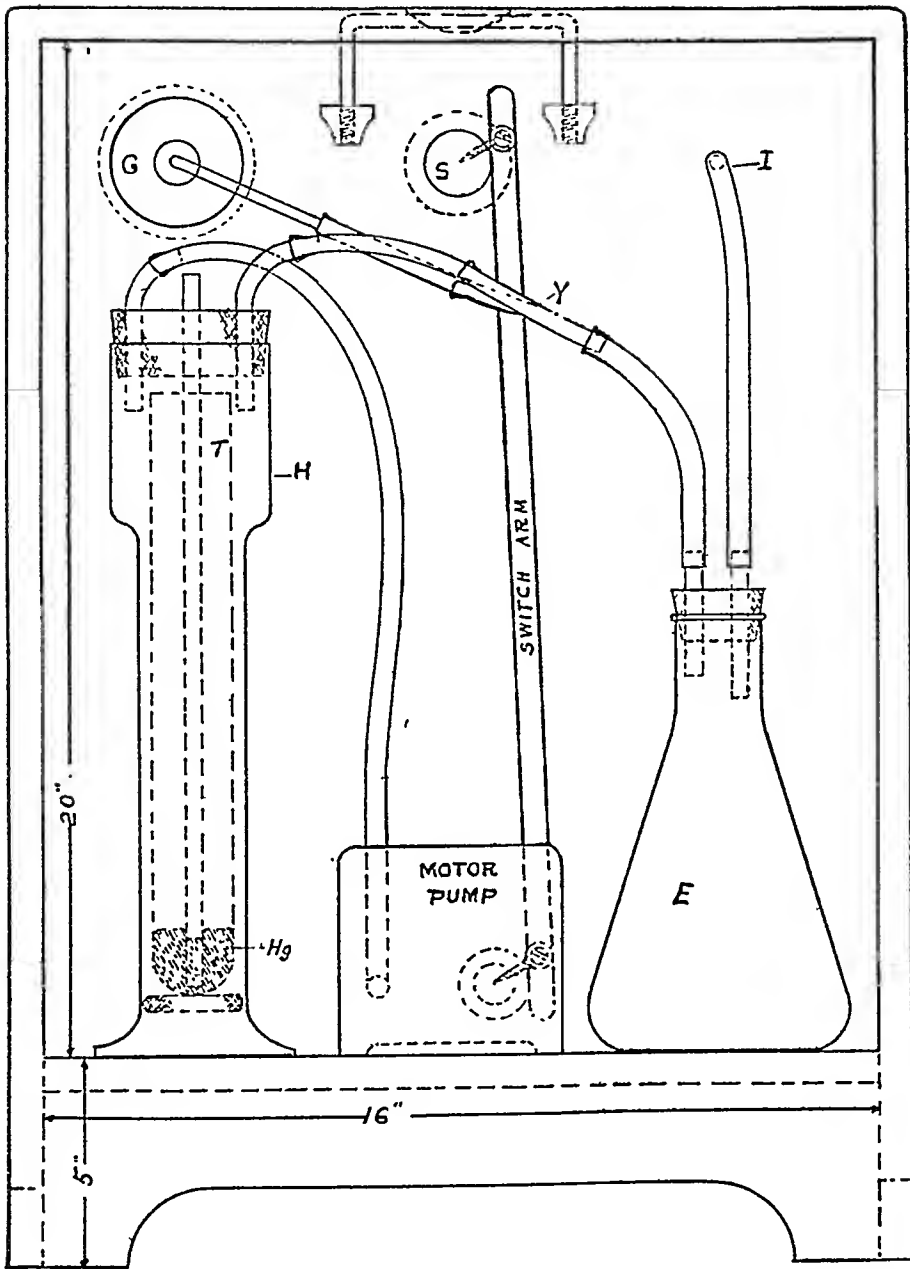


FIG. 2. Drawing of the arrangement of the contents of the cabinet as seen from behind. The motor is controlled by the switch arm from the switch "S" on the front of the cabinet. As air is removed from the system, pressure falls. The pressure is constantly shown on the aneroid manometer "G." The level to which it is possible for pressure to fall is limited by the depth the open tube "T" is placed below the mercury surface. "E" is simply the Erlenmeyer flask which serves as the collector. "H" is the hydrometer jar. A small bit of sponge rubber is placed at the bottom. On this the large test tube rests. Note that both of the short glass tubes through the stopper extend below and outside the mouth of the test tube. At the point "I" the rubber tubing is connected to a short length of copper tubing which goes through to the front of the cabinet.

It is efficient, safe and quiet. In the absence of a leak, either between the cavity and the bronchus or around the catheter, a negative pressure at a constant level may be maintained. All pressure variations in the system are registered by an aneroid manometer.

The parts are standard units of medical and laboratory equipment and thus interchangeable. This fact simplifies repair and maintenance. The power is supplied by a Stedman suprapubic suction pump, which has an ideal motor for this work. The safety valve is provided by extending the end of an open glass tube into a reservoir of mercury. The pressure can be set at any predetermined level by the depth to which the end of this tube is placed below the mercury surface. We usually insert it 1.5 cm. which gives a pressure of approximately minus 20 cm. of water. We have made use of height in the hydrometer jar so as to minimize the possibility of aspirating mercury into the pump, this having been a complication in earlier models.

Below is a list of the more important component parts and our source of supply:

<i>Name</i>	<i>Catalog Number or Designation</i>	<i>Dealer</i>
Stedman suprapubic suction pump.....	#2590	American Cystoscope Makers, Inc. 1241 Lafayette Ave. (Bronx) 59 New York, New York
Aneroid manometer—gauge for Zavod Pneumothorax apparatus.....	#599.4	American Cystoscope Makers, Inc.
Hydrometer jar.....	#6457, 14" tall x 2" diam.	Will Corporation, Rochester, New York
Test tube.....	#16542, 300 x 38 mm.	Will Corporation
Erlenmeyer flask.....	1,000 cc.	
Rubber stopper.....	Size 8	
Rubber stopper.....	Size 13½	

ANATOMICAL STUDIES ON HUMAN TUBERCULOSIS¹

XX. Disseminated Calcified Small Nodular Hematogenous Pulmonary Tubercles, Incidentally Discovered

KORNEL TERPLAN

Comparatively few reports on the condition indicated in the title of this paper have appeared in the literature. It can be expected, however, that the large-scale X-ray examinations carried out in recent years on hundreds of thousands of soldiers and war workers, male and female, will furnish additional information on these findings, sometimes incorrectly referred to as "healed miliary tuberculosis."

Opie and Anderson (1) in a paper entitled *First Infection with Tuberculosis by Way of the Lungs* have shown roentgenograms of 2 lung specimens taken post-mortem (figure 4 on plate 2, and figure 6 on plate 3) with multiple calcified nodules in both lungs in the presence of calcification of bronchomediastinal lymph nodes and calcified tubercles in spleen and liver. These were incidental findings, one in a man twenty-six years of age who died from a recent syphilitic infection, the other in a thirty-six year old woman with staphylococcic septicemia as the cause of death. A few years later, in an editorial on the diagnosis of healed miliary tuberculosis, Opie (2) expressed the view that in the absence of old tubercles in abdominal organs, wide-spread multiple calcified nodules within the substance of the lungs may be the result of healed disseminated tuberculous bronchopneumonia rather than of acute miliary (hematogenous) tuberculosis. Although the anatomical findings in one of Opie's cases, shown in figure 8 on plate 4, with no calcified lesions outside of the lungs and the bronchomediastinal lymph nodes, seemed to justify such a pathogenetic distinction in comparison with the findings in the 2 cases quoted above, the X-ray pictures of the calcified pulmonary nodules were similar in all 3 cases, showing fairly uniform distribution in all lobes.

Whether or not the calcified tubercles shown in figure 6 in the paper by Stivelman and Hennell (3) represent the result of hematogenous dissemination cannot be stated with certainty. The history of extensive pulmonary tuberculosis during adolescence in their case could point to intrabronchial dissemination, responsible for these lesions, rather than to hematogenous seeding. The roentgenogram shows these bilateral calcified tubercles in more irregular distribution with some variations in their size.

Baer (4) found in an eleven year old boy many calcified nodules scattered over both lung fields. There was a history of asthmatic attacks which had started in the wake of measles with catarrhal croup, at one year of age. For the last four years, however, these attacks occurred quite infrequently. The boy was in good health. While an intracutaneous tuberculin, dosage of 0.1 mg., gave a negative result, a subsequent reaction with 5 mg. was positive.

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A roentgenogram very similar to that in the case of Baer, picturing the lungs of a thirty-nine year old white male, is shown by Middleton (5). Middleton found the basal fields more markedly stippled than the apices. The lesions measured from 1 to 3 mm.

Schuermann (6) called attention to isolated pulmonary foci in prolonged hematogenous generalization which, in his experience, were more apt to become caseated than bronchogenic lesions in chronic pulmonary tuberculosis. He did not see conspicuous aspiration tuberculosis from these hematogenous tuberculous nodules which frequently included smaller bronchi. Only very small foci, apparently due to aspiration in the lungs, were found by Schuermann, in contrast to considerable intrabronchial extension in isolated pulmonary tuberculosis (phthisis).

According to Simon (7), in some instances large nodular hematogenous tubercles might form in the course of primary tuberculosis. Although Simon believed that these hematogenous tubercles might eventually lead to cavernous disintegration or to slowly progressive phthisis, he did find scattered calcified nodules in the lungs, as well as sometimes in liver, spleen and omentum, in children who had died from nontuberculous diseases.

Pinner (8), in a paper entitled *Hematogenous Non-miliary Pulmonary Tuberculosis*, stresses the great disproportion of clinical symptoms and physical findings to the amount of the parenchymatous involvement, as seen on the X-ray film, the more or less even distribution of the lesions, the frequent absence of older pulmonary foci from which intrabronchial spread could have occurred, and the frequent association of extrapulmonary lesions with those in the substance of both lungs. Some cases are detected by chance, and the roentgenological involvement of the lungs in these cases is in great contrast to the paucity of disease symptoms. A very characteristic example is pictured in figure 22, showing the X-ray photograph taken in a routine examination of a nurse who had never been ill. In the absence of older upper lobe lesions, such findings were interpreted by Pinner as the result of repeated hematogenous seedings to the lungs.

Sweany (9), in a paper on multiple calcifications, illustrates a striking X-ray finding (figure 2 on plate 1) showing evenly distributed calcareous foci which were thought to be blood-borne metastatic foci formed during the early phase of the primary complex.

That, on the other hand, chronic miliary tuberculous disease might eventually resolve with a very different roentgenological picture is borne out by a report of Rubin (10) on chronic healed miliary tuberculosis. In a patient with innumerable small tubercles in the peritoneal coat, which were incidentally discovered at laparotomy, the chest film disclosed extensive miliary infiltrations in both lungs with about match-head sized tubercles in all lobes and discrete numerous older lesions in the apices. There was a history of tuberculous infection with hemoptysis and pleurisy ten years previously. The recurrence of the disease was apparently conditioned by the state of pregnancy, as the symptoms of peritoneal tuberculosis were noticed one day after delivery. In the course of three years the lung fields, as seen on successive roentgenograms, had

completely cleared. In a subsequent paper (11), however, it is stated by Rubin that sometimes multiple calcified foci are the end-result of hematogenous pulmonary infiltrations. The association with fibrous or calcified tubercles in spleen, liver and kidneys, in the same structural state as in the pulmonary tubercles, was also observed by Rubin in cases of chronic miliary tuberculosis.

That roentgenological evidence of calcified tubercles in the spleen is a diagnostic adjunct in the recognition of protracted hematogenous multiform tuberculosis is stated by Grethmann (12) in a comprehensive report on more than 100 cases dealing with active forms of hematogenous tuberculosis.

According to Miller (13), hematogenous pulmonary foci are capable of absorption in all other parts until only apical and upper lobe foci remain and become calcified. This view of Miller is not to be easily reconciled with the uniform structural appearance of the hematogenous nodular tubercles and the uniform distribution without predilection of the apices, as seen in the X-ray photographs referred to in the papers quoted above. Such "remaining" apical lesions in the cases of Miller were possibly the original source for the hematogenous tuberculosis, rather than having resulted from it.

More recently, Mayoral (14) has commented on multiple miliary calcifications of the lungs. He has seen these shot-like calcified nodules in apparently perfectly healthy individuals with no history of serious past illness. Figure 1 in the paper of Mayoral illustrates a typical picture, showing these calcified pulmonary nodules of uniform size, density and distribution. In the absence of any history of disease in the patient, these multiple calcifications are not considered as the end-stage of acute miliary tuberculosis by Mayoral. In cases of healed miliary disseminated bronchopneumonia, however, there is, according to Mayoral, an unmistakable history of previous tuberculosis or one quite suggestive of this condition. Also, in persons with such a history, the nodules on the roentgenogram were found to appear more irregular in shape and distribution and in various stages of calcification, pointing to some difference in their structural age. Whether or not these latter morphological features alone are of such a distinctive pathogenetic significance will be discussed on the basis of our own anatomical analysis.

Blaine (15), already in 1924, had reported 3 instances with multiple calcified nodules in both lungs disclosed by X-ray. They were seen in white males, thirty-six, thirty-four, and twenty-four years old. The lung tissue between the calcified tubercles showed normal transparency. In all 3 cases, however, there was a definite history of active pulmonary tuberculosis.

From the foregoing citations it appears that the roentgenograms in the cases of Middleton, Baer, Pinner, Sweany and Mayoral represent almost identical conditions. In all of them there was no history of previous pulmonary tuberculosis. They were seen in apparently healthy persons. In contrast, in Rubin's case quoted above the hematogenous miliary seeding to both lungs in a patient suffering from tuberculosis had eventually completely cleared without leaving any trace, fibrous or calcified, which could have been detected on the roentgenogram.

In the course of our studies 2 observations were made of disseminated calcified

nodular tubercles in fairly symmetrical distribution in both lungs, of obviously hematogenous character combined, in one of these cases, with calcified nodules in liver and spleen. It is the entire morphological picture which we wish to present briefly. It gives detailed histological proof, thus far missing, of this peculiar condition, as startling in its radiographical appearance as it appears harmless in its clinical significance.

Case 1: (B. G. H. 3060) A sixty year old farmer from Eden, New York was struck by an automobile and suffered several fractures of the right tibia, right fibula, seventh cervical and seventh to tenth thoracic vertebrae, and of the frontal bone with lacerations of the frontal lobe. He died four hours after the accident in a shock-like condition.

Postmortem examination revealed the typical picture of massive fat embolism of the pulmonary arteries (16), with marked recent emphysema. Only the lateral lower portion of the right upper lobe and the lateral subpleural areas in the left lower lobe appeared moderately collapsed. There were no pleural adhesions. Many calcified nodules were felt by the palpating finger in all lobes; considerable calcification of the bronchopulmonary and tracheobronchial lymph nodes on both sides was noticed grossly. Other findings of tuberculosis included: scattered calcified tubercles in the spleen, which was atrophic, and in the liver; a few small fibrous tubercles in both kidneys; and very distinct, fairly firm caseation of the mesenteric lymph nodes. The roentgenogram of the undissected lungs with the bronchomediastinal lymph nodes is shown on plate 1. The X-ray photograph of the spleen revealed about thirty calcified tubercles from 0.5 to 4 mm. in diameter. Some of these were of stony consistency. The lymph nodes along the body and about the head of the pancreas contained a few small chalky and calcified tubercles from 1 to 2 mm. in diameter. The roentgenogram of the liver showed comparatively few calcified nodules of about 1 mm. thickness. There was no gross nor roentgenological evidence of chalky or calcified changes in the caseated mesenteric lymph nodes. Nor was there any gross or radiological evidence of tubercles in the wall of the intestinal tract. Careful inspection of the entire wall of the intestinal tract did not reveal mucosal tubercles nor scars which could have been detected with the naked eye.

There was no history of a tuberculous disease. The relatives of the deceased stated emphatically that this farmer had always enjoyed the best of health. No tuberculin test was done at any time and there was never any need for an X-ray examination during his entire life.

Histological report: In this case all nodular pulmonary lesions were examined, including the lymph nodules in the substance of the lungs; and many sections were cut from all bronchopulmonary, tracheobronchial and angulus lymph nodes of both sides; also, sections from the spleen, liver, kidneys and various parts of the small intestine. For the purpose of proper localization and identification, both lungs were divided into nine fields. The individual nodules in each field were marked with the letters of the Latin alphabet. In three areas (right middle lobe, upper half of the right lower and lower half of the left lower) the large number of calcified tubercles made the addition of a few Greek letters necessary. This was naturally a quite exhaustive study, but the reader will be spared from the detailed report on each individual lesion, as given in the original histological description. In addition to the numerous parenchymatous tubercles, there were intrapulmonary lymph nodules found in each lung, entirely replaced by fibrous, fibrous-chalky or chalky-calcified changes. On the other hand, there were a few subpleural lymph nodules in each lung with no tuberculous changes whatsoever. A few bronchopulmonary lymph nodes in the hilar interlobar portion of both lungs proved likewise to be free of tuberculosis. The great majority of the calcified and chalky tuber-



L

cles, as pictured in the roentgenogram, were in the parenchyma of the lung. Only in very few completely hyalinized fibrous nodules could it not be decided whether they were minute obliterated lymph nodules or completely hyalinized parenchymatous tubercles. There was comparatively little anthracotic pigmentation in the lungs and lymph nodes, as the deceased had spent all his life in the country.

For the convenience of the reader, we have summarized our histological findings of the parenchymatous tubercles as follows: there were ninety-five calcified or chalky-fibrous tubercles altogether in the left lung, varying in diameter from 0.5 to about 5 mm. The majority of them measured from 1.5 to 3 mm. Two were firm stones surrounded by complete osseous rings; in five there was incomplete marginal bone formation; while one was a bony fibrous lesion; thirty-three were in a firm stony state surrounded by hyalinized fibrous rings; twenty-two were in a stony chalky state; and nineteen appeared more chalky, with much lipoid-containing detritus and comparatively thick fibrous walls. Finally, there were thirteen fibrous, firm nodules without chalky or stony matter.

In the right lung the structure of the eighty-three parenchymatous lesions was as follows: four in firm stony state with thin but complete bony ring; eight about of equal size with only localized marginal bone formation; thirty-three firm stony foci; twenty-two chalky calcified lesions; and six chalky fibrous lesions with a great deal of lipoid debris in the centre and compact hyaline walls. There were ten hyaline-fibrous nodules with minimal or without any central chalky detritus. In general, there were a few more chalky calcified nodules in the basal portions, especially on the right side. The few lesions with the oldest structural appearance were in the hilar area of the right lung and in the upper and lower half of the left lower lobe. Whether all or only part of these few nodules were the actual primary foci, formed simultaneously, or whether some of them had resulted from focal extension in the early phase of the primary infection, is impossible to state. The gross, histological and radiological appearance of the bronchopulmonary- and tracheobronchial lymph nodes would point to at least two primary complexes, one in each lung.

Plates 2 and 3 demonstrate the histological structure of some of these tubercles in various stages of regression. A brief description of these lesions will be given.

Plate 2 pictures six parenchymatous lesions from the left lung:

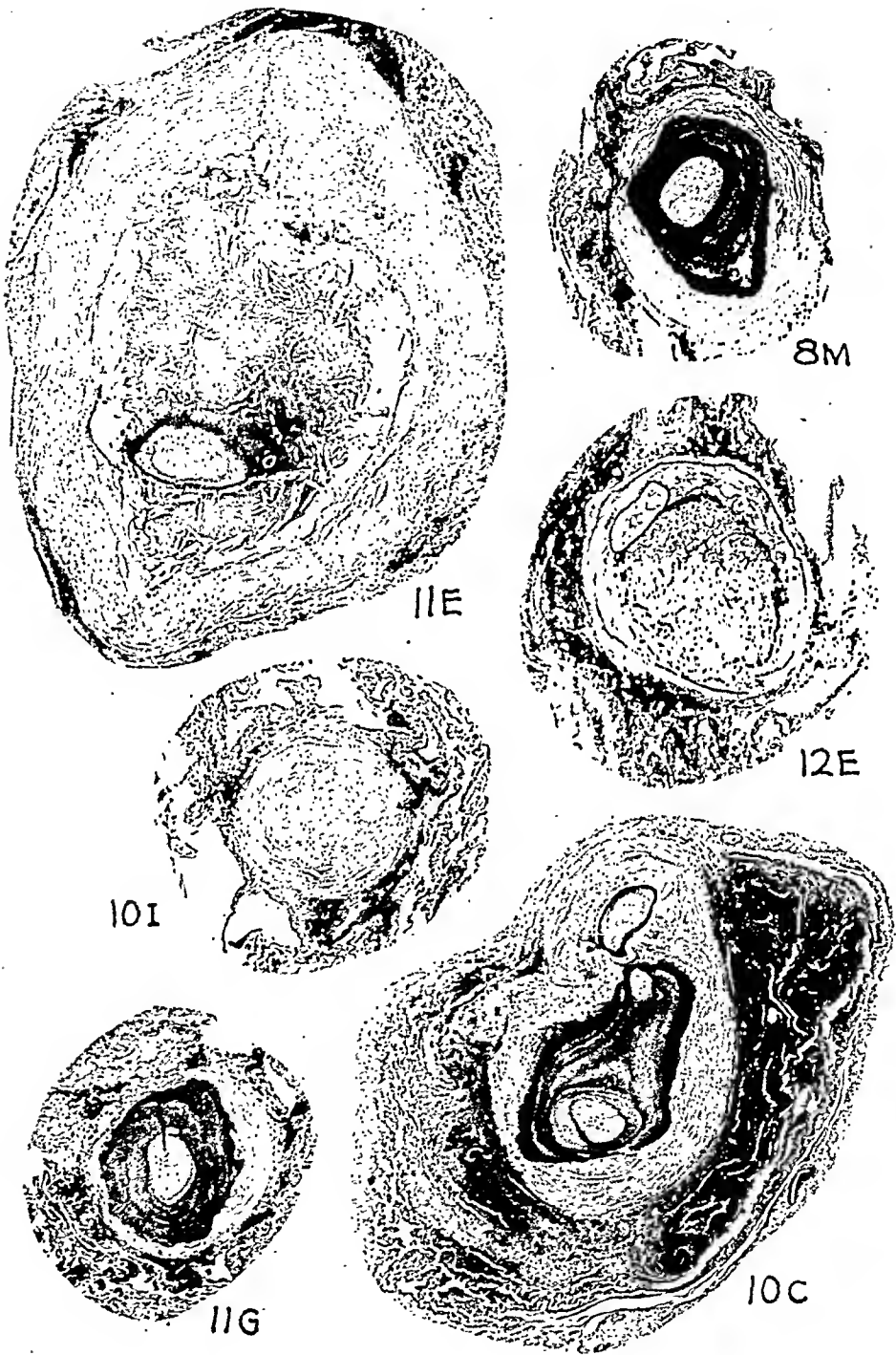
12 E, lower half of left lower lobe—This is a typical picture of an obsolete firm stony primary focus surrounded by a fairly thick osseous shell, with some fatty and lymphoid marrow. Note the well preserved alveolar pneumonic pattern in most of the stony core of the lesion; also the almost complete transformation of the original hyaline wall into bone tissue.

11 G, upper half of left lower lobe—Firm stone with an almost complete but relatively thin bony shell attached to a firm hyaline wall, with collections of histiocytes and fibroblasts between the bone tissue and the hyaline capsule. Note the few cholesterol crystals included in the firmly calcified core of the lesion.

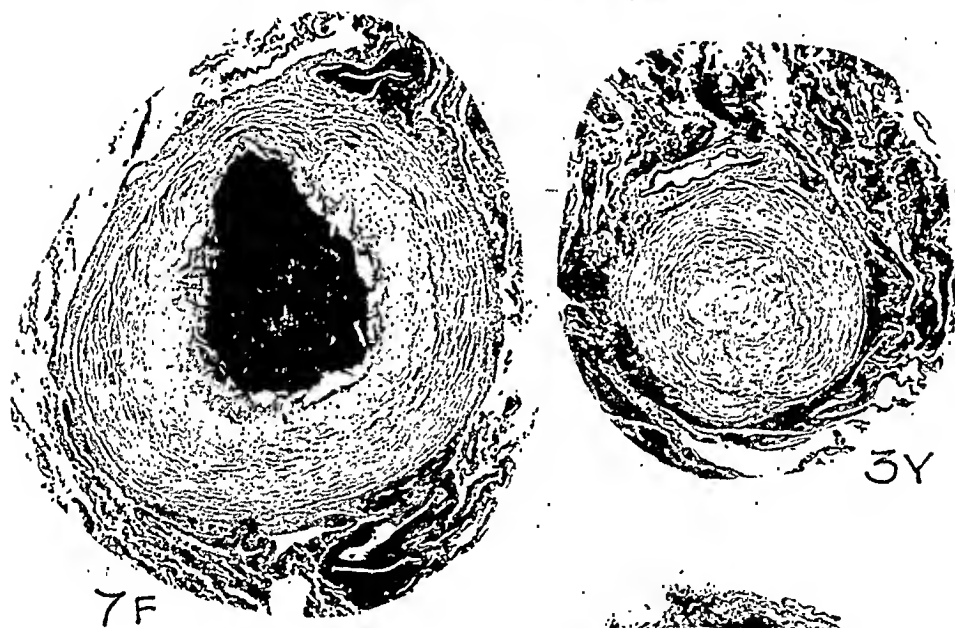
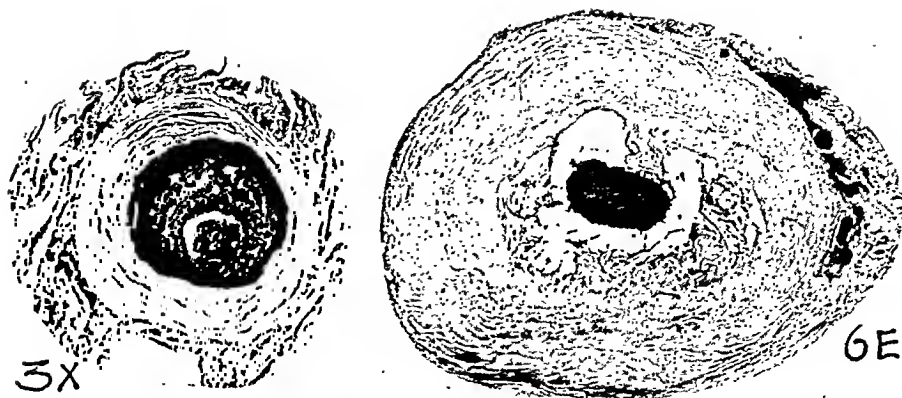
8 M, upper half of left upper lobe—Calcified stony tubercle with a slightly less opaque centre, firmly encased within a hyaline capsule. There is already evidence of some loosening of its hyaline texture.

10 C, lower part of left upper lobe—This is a slightly larger, firmly calcified tubercle within a thick hyalinized capsule. Very early phases of bone formation between the calcified core and the thick hyaline capsule can be noticed in the upper portion of the pear-shaped stone.

11 E, upper part of left lower lobe—This is a relatively large chalky lesion containing masses of cholesterol needles and chalky and slightly calcified debris around a small



Left Lung



Right Lung

centre, which appears still firmly caseated. Note, again, the very thick hyaline fibrous capsule, gradually blending with the chalky lipid-laden nucleus.

10 I, lower part of left upper lobe—Firmly hyalinized nodule (in decalcified state) with considerable proliferation of fibroblasts and some histiocytic elements, apparently a state of accomplished organization of a small central chalky-calified core.

On plate 3, corresponding tubercles from the right lung in different stages of regression are shown:

1 H, upper part of right upper lobe—A firm stony tubercle with the alveolar pneumonic structure faintly preserved, surrounded by an almost complete bony shell within a hyaline-fibrous capsule. This latter is still fairly thick, its inner portion near the bony ring slightly edematous, with active fibroblasts merging with the newly formed osseous capsule.

3 R, hilar level of right upper lobe—Relatively large hyalinized calcified and in part ossified tubercle with two firmly calcified portions separated by hyalinized and distinctly calcified fibres. Note the oblong portion in the upper field of the focus with part of the calcified core replaced by lymphoid and some fat marrow, containing a moderate number of plasma cells and well filled capillaries. The remainder of this old stony lesion is entirely replaced by a bony shell around the marrow, while the upper portion of the same focus shows the comparatively thin and incomplete bony ring firmly attached to the calcified core, in which cholesterol needles are firmly included. In the lower part of this large focus there is a second firm stone with some cholesterol needles included, but without any bone formation. The remainder of the focus consists of firm collagenous, edematous fibres.

3 X, hilar level of right upper lobe—There is a firm stone including a few cholesterol needles, with typical Liesegang rings within a distinct collagenous capsule, the inner part of which is somewhat edematous and contains a good number of fibroblasts. There is apparently also some resorption of lipid around the stony centre.

7 F, base of right lower lobe—A fairly large focus with an ovoid calcified-chalky central core, with considerable calcified matter especially in the outer portions of the lesion. Note in some portions of the thick hyaline capsule a very clear differentiation into two parts, a more compact garland-like inner portion gradually blending with the chalky and calcified debris, and a firmer and distinctly hyalinized outer ring which, however, at some points has replaced entirely the inner layer and seems to fuse with the calcified core. Within the zone between the chalky-calified core and the compact inner mesenchymal layer there is some fibrinoid exudate, necrobiotic debris and some brownish pigment-dust.

6 E, upper portion of right upper lobe—This is a chalky-fibrous lesion with little calcification in the centre. Part of the lipid debris and some chalky matter has fallen out of the centre. Note this debris with cholesterol needles gradually blending with the hyaline capsule. Here, again, in some areas an inner ring-like zone, comparatively compact, can be made out, containing pigment-laden macrophages. The outer capsule is more markedly hyalinized.

3 Y, hilar level of right lung—Completely hyalinized nodule with the centre apparently corresponding to firmly organized, originally chalky matter. This appears as a later state of the changes shown in 6 E.

Various intermediate phases between stages, as pictured in 6 E and 3 Y, could be observed among the chalky-fibrous nodules in both lungs, including small hyalinized nodules in which still a chalky-lipid core had remained. The larger foci especially—between 4 and 5 mm. in diameter—showed this gradual organization of the chalky, lipid-laden and partly calcified core. In these most of the centre consisted of chalky and lipid debris, while in the thick collagenous wall sometimes a clear differentiation

into an inner and outer layer could be seen, apparently corresponding to the "specific" and "nonspecific" capsule in the so-called "reinfects" of Puhl. It is evident from the brief description given on some of these nodules that these two zones are only temporary phases in certain regressive stages of predominantly firm chalky character, and therefore frequently a more or less intimate blending of the two capsules might be observed. Occasionally, very close to a calcified stony parenchymal focus encased within a fibrous wall, a subpleural lymph nodule with calcification in its centre was found in the same slide. Wherever a bony band had formed around a firm stone, the immediately surrounding portion of the original hyaline wall was of somewhat looser texture as compared with its outer part. Closely attached hyaline tubercles (in so-called satellite fashion) were seen around only few calcified or chalky-calcified foci. In some firm stony foci with more or less complete thin osseous shell the centre appeared less compact. In the larger parenchymatous foci, in a chalky-calcified state, the break-up of the central portion by gradual ingrowth of connective tissue could be observed, causing peculiarly shaped fragments. In these stages there still is a considerable amount of cholesterol debris between the mesenchymal wall and the chalky-calcified centre. It is around such foci that part of the hyaline wall in the inner zone appears as a special compact band, here and there containing a rare small Langhans giant cell and shadows of epithelioid cells.

Figure L on plate 1 shows a section through one of the lymph nodes in the right venous angle. Magnification is about $7\times$. Note the large calcified and in part still chalky tubercles, more or less firmly encased by hyaline-collagenous walls.

The lymph nodes on both sides, including the bronchopulmonary, tracheobronchial and paratracheal groups, showed almost identical changes. There was considerable calcification with calcified or chalky-calcified conglomerate tubercles within thick hyaline walls, combined with formation of smaller stones entirely surrounded by hyaline capsules, with or without chalky material included. In others, true stone formation was less conspicuous. Most of the lymphoid structure here was replaced by extensive chalky-calcified masses surrounded by hyalinized conglomerate tubercles. In some tracheobronchial lymph nodes, especially on the right side, there were some differences in the tuberculous structures insofar as a few lymph nodes contained only hyalinized-chalky, fairly large conglomerate tubercles, but no stones; while in others of the same group complete calcification was noted with some chalky detritus within hyaline capsules. As seen in the X-ray photograph on plate 1, there is hardly any difference in the opaque whitish shadows pointing to extensive calcification and chalky changes in the various lymph node groups draining both lungs. The lymph nodes in the left venous angle, however, did not show stone formation. They contained for the most part firm, fibrous conglomerate tubercles and only minimal chalky material. Also, in some bronchopulmonary lymph nodes, especially on the right side, one was impressed by large, chalky and fibrous tubercles without any stone formation. There was a good deal of lipid detritus in the centre of these tubercles. In a bronchopulmonary lymph node at the hilum of the left lower lobe, smaller hyalinized-fibrous or completely hyalinized tubercles with some calcified detritus in the centre were seen. Occasionally an epithelioid cell tubercle with a Langhans giant cell still could be recognized in the inner zone of the fibrous wall. On the other hand, in an intrapulmonary lymph node at the right hilum level, unusually firm stone formation was noticed with no clear evidence of ossification, but with still large sheaves of cholesterol needles included within this firmly calcified substance.

An analysis of the histological lesions observed in the bronchomediastinal lymph nodes shows, in general, not a uniform structure as usually found in so-called "closed com-

plexes" in which the lymph node changes are in a uniformly calcified or fibrosed state. Here, in practically all groups there was a combination of older stony lesions with calcified-chalky or only chalky changes or, again, with small fibrous conglomerate tubercles. In addition, in a few bronchopulmonary lymph nodes some still active tuberculous granulation tissue was noticed.

In our previous paper on focal extension (17) attention was called to the occasional occurrence of isolated foci apart from the primary focus, of the same histological structure and apparently of similar structural age as the primary focus. This latter conclusion was based on a few cases in which these foci were found in comparatively recent stages of evolution or regression. In a few of these, especially in the presence of hematogenous tubercles in such organs as spleen and liver, it was suggested that these additional lesions of primary-focus character had formed by focal hematogenous extension.

It was of considerable interest, therefore, to analyze carefully the structure of the multiple tubercles in this case. Neither from the gross picture nor on the basis of the X-ray photograph was there any possibility to point to the true primary focus or foci in each lung. Practically all the tubercles in both lungs were of the size range which frequently is seen in the majority of true primary foci (from 1 to 5 mm. in thickness). Clear evidence of hematogenous tubercles in spleen, liver and kidneys, and the uniform and almost symmetrical distribution of the tuberculous nodules in each lung seemed to point to hematogenous spread as the pathogenetic mechanism. The structural distinctions, however, found in the various parenchymatous tubercles made it quite clear that all these pulmonary nodules could not be of the same age. Together with the histological findings in the bronchomediastinal lymph nodes they seemed to indicate several episodes of a hematogenous spread not limited to the early phase of the primary complex. It is most likely that the original source for this repeated spread was the extensive tuberculous changes within the bronchomediastinal lymph nodes.

Nowhere in the lungs were there lesions pointing to true exogenous reinfection or superinfection, and no apical scars. Indeed, the apical and subapical areas appeared more sparsely affected by the nodular dissemination than the hilar and basal areas of both lungs. The roentgenogram shows clearly that there was definitely no predilection for the apical areas. The nodular tubercles everywhere in the lungs were well encapsulated. Nothing pointed to the typical acinous pattern so characteristic of bronchial and peribronchial spread. Nor was there any conspicuous perifocal fibrosis, as so frequently is seen between older subapical obliterated bronchial tubercles. The small hyalinized satellite tubercles were comparatively rare, seen within or close to the capsule of but a few parenchymatous tubercles. The various structural stages, ranging from a soft chalky-fibrous tubercle to a hard stone, as well as small differences in size, ranging from less than 1 to 5 mm., can be interpreted as the results of repeated hematogenous seeding in connection with protracted lymphogenous progression within the lymph nodes of the original primary complex or complexes. Such

differences in the structural age of parenchymatous tubercles or the limited variations in size, as found in our case, are in themselves no sufficient proof of an intrabronchial as against a hematogenous route. It was pointed out that most of the bronchomediastinal lymph nodes showed a more or less intimate combination or fusion of more obsolete stony and less old chalky-fibrous lesions in a few areas with persistence of active tuberculous granulation tissue.

The finding of extensive cascated lesions in the mesenteric lymph nodes can be best interpreted, we believe, as the result of a true exogenous superinfection. There was no evidence of hematogenous or deglutition tuberculosis in the wall of the intestine. The anatomical appearance of the tuberculous changes in the mesenteric lymph nodes made the impression of a comparatively recent lesion with no calcification or chalky changes, as disclosed by the X-ray film. That these lesions in themselves might furnish an additional source for hematogenous tubercles is possible; whether or not it has occurred in this case is difficult to state. Apart from the caseated mesenteric lymph nodes, there was no recent caseated tuberculosis present anywhere in the body, although a few small fibrous tubercles found in the lungs might have formed in a relatively short time from organization of caseous lesions. The bulk of the nodular tubercles in the lungs had decidedly an older structural appearance than the caseated mesenteric lymph nodes. There are no direct orthograde routes between the peripancratic lymph nodes and the lower group of the mesenteric nodes; therefore, the source for the tuberculosis of the mesenteric lymph nodes was, in all probability, outside of the pulmonary lesions or the splenic and hepatic hematogenous tubercles.

The anatomical picture, as incidentally found in this case, is not the end-stage of a true picture of miliary tuberculosis. In this respect we fully agree with Mayoral. Such a view is supported by the negative histories relative to tuberculosis in the cases previously quoted (Middleton, Baer, Pinner, Sweany, Mayoral). On the basis of our present knowledge of true miliary tuberculosis, especially in the subacute and protracted types, it is more likely that this actual miliary dissemination clears by fibrous organization, as the size of these lesions is as a rule distinctly below the nodular hematogenous tubercles seen incidentally in healthy individuals. On the other hand, in cases of prolonged hematogenous tuberculosis with chronic lesions in extrapulmonary organ systems in particular (as in the skeleton or in the genital tract) it is possible that selected hematogenous seeding to the lungs might produce isolated nodular tubercles which frequently involve smaller bronchi without, however, leading to further intrabronchial spread. It is most probably this type of lesion which in later stages would appear as nodular scattered calcifications, which were apparently seen by Rubin. Their hematogenous nature, in the caseated state, has also been stressed by Schuermann. Whether or not some of the larger lesions (4 to 5 mm.) found in our case might have furnished a source for localized focal intrabronchial spread, while they still were in a recent state, cannot be determined.

In analyzing microscopic sections taken through various portions of the small intestine, a very interesting peritoneal reaction was observed. This, we believe,

supports the view expressed above, that the caseation of the mesenteric lymph nodes was comparatively recent. There was a very distinct thickening of the serous coat with considerable activation of young fibroblasts and some histiocytes, but without real fibrosis. This cellular infiltration extended somewhat between the interstices of the muscle layers. There was no noteworthy change in the inner layers apart from slight edema. Whether we are dealing here with a subsiding peritoneal reaction to fluid already resorbed or to a collateral non-specific response in connection with the distinct enlargement and firm caseation of the mesenteric lymph nodes is difficult to state. There was no specific tuberculous tissue reaction in the inflamed peritoneal coat.

As it frequently happens with unusual cases, about at the same time a second similar observation was made postmortem, incidentally, in a fifty-five year old white male (B. G. H. 3070). It is definitely stated in the patient's record that he had always been in good health. There was, in particular, no history of tuberculosis at any time. He died from a postoperative paralytic ileus following bilateral herniotomy. This case was not studied in any way comparable with the former. The roentgenogram of the undissected specimen is shown on plate 4. Some of the calcified nodules were readily palpated when the lungs were removed. Several sections cut through spleen, liver and kidneys failed to disclose grossly noticeable tubercles. The lungs were not adherent. Again, the lower lobes and the right middle lobe contain more of these multiple calcified nodules than the apical portions of the upper lobes. Extensive calcification of the bronchomediastinal lymph nodes seemed to point to at least two primary complexes. There was no detailed histological study in this case. As the history with regard to tuberculosis was entirely negative, we feel that even in the absence of calcified tubercles in such organs as spleen and liver (small fibrous tubercles might very easily have been overlooked) the symmetrical distribution of the tuberculous nodules in both lungs, in the absence of any lesion which could have furnished the source for intrabronchial aspiration, might represent the result of protracted hematogenous dissemination to the lungs in connection with the primary complexes.

The detailed histological analysis of the first case has proved beyond any doubt that among all the multiple calcified and chalky nodules there are old, nearly obsolete and less old chalky-fibrous tubercles. There are no calcifications from some other cause which could produce the picture as described. This will be shown, in addition, in a subsequent paper dealing with nontuberculous calcifications and ossifications. On the basis of all available clinical and the—so far scarce—anatomical evidence, this picture of multiple calcifications is not considered to represent later stages of a previously actively progressive tuberculous disease, and definitely not of true miliary tuberculosis. It is more likely that these lesions are the result of repeated, clinically harmless, hematogenous seedings in connection with protracted lymphogenous progression. It is a well known fact that most primary infections with tuberculosis are established without the individual being in the least aware of it. That during the active phase scattered hematogenous tubercles are formed, especially in the spleen and liver but sometimes also in the lungs, usually of small miliary size, has been repeatedly demonstrated by incidental postmortem findings. On the basis of the detailed

histological analysis of our first case presented here, and from the available clinical roentgenological data referred to, we wish to add that such hematogenous seeding does occur, apparently also occasionally in later phases of the primary

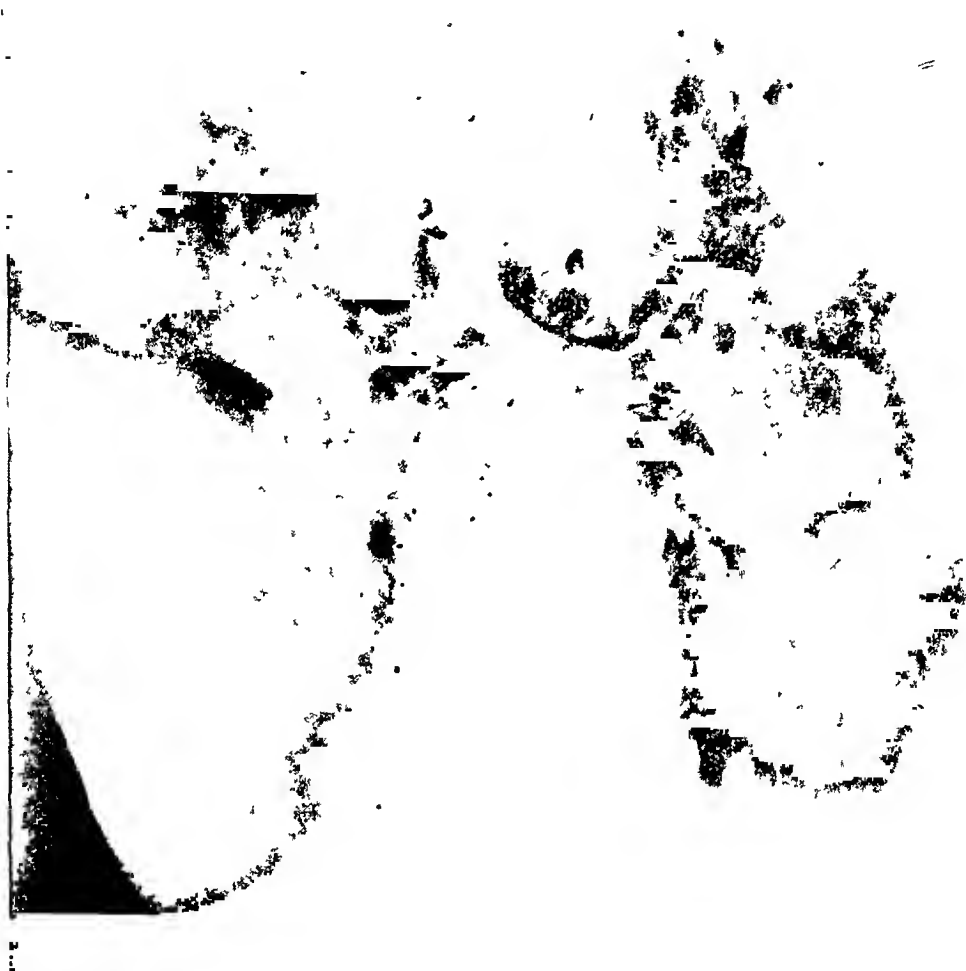


PLATE 4

complex, in connection with protracted lymphogenous progression or exacerbation, without, however, leading to actual clinical disease.

SUMMARY

An incidental postmortem finding in a sixty year old white farmer, who was said to have been always in the best of health and who was killed accidentally, revealed nearly 200 parenchymatous calcified and chalky tubercles in fairly even distribution in both lungs, with no predilection of the apical and subapical areas, in the presence of multiple calcified and fibrous tubercles in liver, spleen

and kidneys. The results of the histological analysis of all parenchymatous lesions, intrapulmonary lymph nodules and both bronchomediastinal and venous angle lymph node groups are presented. The histological structure of the individual parenchymatous lesions does not permit any unequivocal interpretation in terms of pathogenesis without considering the anatomical picture in its entirety. The reported findings differ from those in "focal extension." The complete histological analysis of the parenchymatous pulmonary tubercles has disclosed various distinctive stages of structural regression between the soft chalky-fibrous, the chalky-calcified and the firm stony and calcified-ossified state. Together with the changes in the bronchomediastinal lymph nodes, representing also various combinations of older and less old and possibly still active tuberculous lesions, they seem to point to protracted lymphogenous progression with repeated phases of hematogenous spread, leading to symmetrical dissemination of small nodular calcified and chalky-fibrous tubercles in both lungs. These parenchymatous pulmonary tubercles represent the anatomical substrate of a few roentgenological chance observations in apparently healthy individuals with no known history of tuberculous infection or disease, as reported in the more recent tuberculosis literature.

SUMARIO

Un hallazgo autopsico fortuito en un labrador blanco de 60 años, que según se dijo había disfrutado siempre de la mejor salud y había muerto en un accidente, reveló casi 200 tubérculos calcificados y cretáceos distribuidos con bastante uniformidad en el parénquima de ambos pulmones y sin predilección hacia las zonas apicales y subapicales, en presencia de muchos tubérculos calcificados y fibrosos en el hígado, bazo y riñones. Preséntase el resultado del análisis histológico de todas las lesiones parenquimatosas, los ganglios linfáticos intrapulmonares y de los grupos tanto del broncomediastino como del ángulo venoso. La histología de las distintas lesiones parenquimatosas no permite ninguna interpretación explícita en términos de patogenia sin considerar el cuadro anatómico total. Los hallazgos comunicados discrepan de los encontrados en la "extensión focal." El completo análisis histológico de los tubérculos parenquimatosos pulmonares reveló varias etapas distintas de regresión histológica entre el período creto-fibroso, creto-calcificado y el firme período pétreo y calcificado. Junto con las alteraciones en los ganglios linfáticos broncomediastínicos, que representan además varias combinaciones de lesiones tuberculosas antiguas o menos recientes posiblemente todavía activas, parecen mostrar avance linfógeno prolongado con fases repetidas de propagación hematógena, que conducen a la diseminación simétrica en ambos pulmones de tuberculillos nodulares calcificados y creto-fibrosos. Estos tubérculos pulmonares parenquimatosos representan la base anatómica subyacente de algunas observaciones roentgenológicas fortuitas en individuos aparentemente sanos sin antecedentes conocidos de infección o enfermedad tuberculosa, que han aparecido en la literatura más reciente de la tuberculosis.

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A COMPARISON OF THE TUBERCULIN PATCH TEST AND THE COLLODION-TUBERCULIN TEST¹

PAUL SINGER, JOSEPH J. SOTTILARO AND HERMANN VOLLMER

In an attempt to simplify the tuberculin patch test (1), one of us (V.) made a number of experiments with a collodion-tuberculin emulsion in October, 1941. Equal parts of standard Old Tuberculin and U.S.P. collodion were vigorously shaken. An emulsion of tuberculin in collodion resulted with collodion as the continuous phase as evidenced by the fact that a drop of the emulsion readily dissolved in collodion but not in water. Figure 1 represents a microphotograph of such an emulsion, magnified 546 times.

Persons highly sensitive to tuberculin showed a positive skin reaction within thirty-six to forty-eight hours following the application of this emulsion. Further experimentation, however, revealed several disadvantages of this method:

- 1: It takes ten or more minutes for the tuberculin-collodion film to dry on the skin. Children have to be watched for this time lest they wipe off the substance.
- 2: The dried tuberculin-collodion film peels off the skin after a variable length of time; some films adhere for a few hours only, others for forty-eight hours; in most instances a significantly large part of the film peels off. Thus the time and extent of contact between skin and tuberculin is not uniform which by necessity leads to uneven results.
- 3: The volatile solvents of the collodion evaporate whenever the bottle is opened. Consequently, the collodion-tuberculin undergoes continuous changes. The proportion between the nonvolatile tuberculin and the volatile collodion solvents increases and the physical state of the emulsion is altered until so much of the solvent has evaporated that pyroxylin precipitates.

For these reasons the collodion-tuberculin test was not thought to be satisfactory and the experiments were discontinued.

Recently Corper (2) aroused considerable interest in this form of test by introducing his "transdermal test." The test substance is an emulsion consisting of Corper's (3) autolytic tuberculin and a plastic substance diluted in a volatile solvent. The proportions as well as the nature of the plastic substance and solvent are not revealed. A comparative study of the Corper test and the tuberculin patch test, when combined with roentgenographic examinations, may decide which of the two tests is more satisfactory in case-finding, that is, in the separation of infected from noninfected cases. However, two different tuberculins and two different methods of applying tuberculin would be simultaneously compared in the same study. The outcome of the comparison would therefore neither decide on the comparative quality and strength of the two different tuberculins nor on the comparative value of the two test methods.

A fair evaluation of the two test methods as such calls for the use of the same tuberculin applied by the two different methods which are to be compared. We

¹ From the Hudson County Tuberculosis Hospital, Jersey City, New Jersey, B. S. Pollak, M.D., Medical Director.

therefore asked the Lederle Laboratories, Pearl River, New York, to make from the same batch (Nr. 61-1) of tuberculin, grown on a synthetic medium and having four times the potency of standard Old Tuberculin, (A) Lederle-Vollmer tuberculin patch tests, and (B) a mixture consisting of 50 per cent U.S.P. collodion and 50 per cent tuberculin (batch Nr. 61-1).

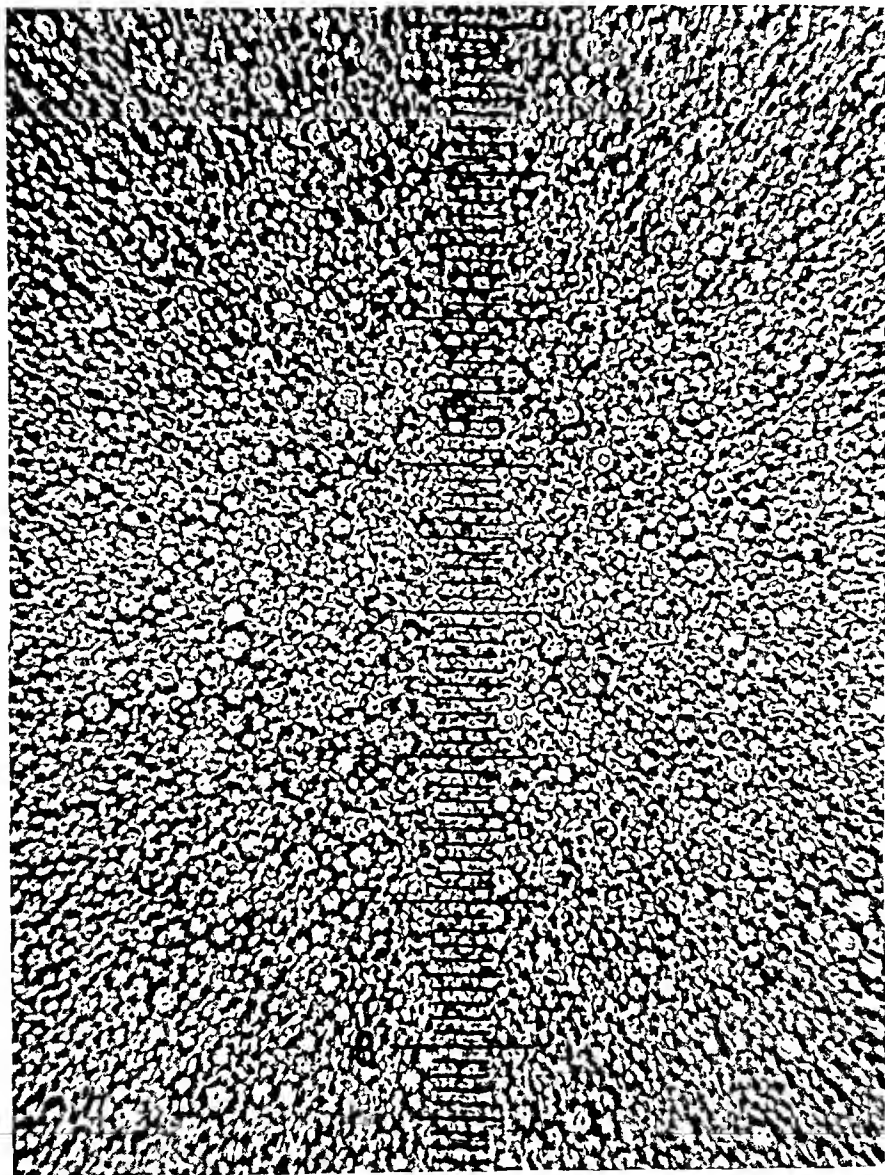


FIG. 1. Microphotograph of an Old Tuberculin-collodion emulsion in a 546 times magnification.

This latter composition was freshly prepared, kept on ice in tightly closed bottles and emulsified by vigorous shaking before use. A good but not stable emulsion results which dries within ten minutes on the skin and forms a continuous film. However, after the emulsion has been used for a while and the

bottle repeatedly opened, some precipitation of pyroxylin takes place, probably due to partial evaporation of its solvents. This change interferes with the formation of continuous films on the skin and the drying takes longer than ten minutes. Addition of ether restores the original quality of the emulsion.

We tested 213 well studied patients between 6 and 65 years of age, the majority having arrested tuberculosis. With the exception of 4, all had in the past an active episode and were successfully treated with collapse therapy; most of their tuberculous processes were, at the time of this study, arrested for an average of from two to four years. All patients were under supervision by fluoroscopy, were X-rayed at least every four months and their sputa were examined monthly by the concentrated smear and culture methods. Most of the patients were out-patients and working. Only 8 patients with active processes were included.

TABLE 1

	CASES	ACTIVE TUBERCU- LOSIS	ARRESTED TUBERCU- LOSIS	NO TUBER- CULOSIS
Total	213	8	201	4
Reactions to tuberculin patch test				
Positive	191	8 (100%)	183 (91%)	0
Negative	21	0	17	4
Erythema	1	0	1	0
Reactions to tuberculin-collodion test				
Positive	44	2 (25%)	42 (20.9%)	0
Negative	162	6	152	4
Erythema	7	0	7	0
Positive reactions to collodion control . .	6	0	6	0
Patch test positive, collodion test negative	141	6	135	0
Patch test negative, collodion test positive	0	0	0	0

The skin areas were cleaned with acetone. The patch test was applied to one forearm and a drop of collodion-tuberculin was placed upon the inner surface of the other forearm. The collodion was spread over an area 1 cm. in diameter by means of a glass rod and allowed to dry for at least ten minutes. In each case a collodion control with plain U.S.P. collodion was done. Both tests and the control were applied at the same time and removed forty-eight hours later. The reactions were read twenty-four hours after the removal of the tests. This early reading, twenty-four hours before the usual time, probably diminished the number of positive reactions, but was thought to bring out clearer the difference, if any, of time required to react to either test. It must be borne in mind that with the collodion-tuberculin test tuberculin is applied to the skin

in fluid droplets from the onset. With the tuberculin patch test some time elapses until the dry tuberculin is so much liquefied by insensible perspiration that the skin may react to it. For this reason it was anticipated that skin reactions may appear earlier with the collodion-tuberculin than with the tuberculin patch test.

The degree of positive reactions was recorded in gradations from 1 to 4 plus, and as erythema without induration. The latter represented either questionable or pseudoreactions. The cases showing 1 to 4 plus reactions were grouped together as positive in the final tabulation (table 1).

RESULTS

Of the 213 patients, 191 showed a positive reaction to the patch test, while only 44 were positive to the collodion test. The patch test reactions were usually more clear-cut and stronger than the reactions to collodion-tuberculin. The reactions to the latter consisted in several cases of merely one or two lichens which were difficult to interpret and sometimes only verifiable on the basis of a clear-cut patch test reaction on the other arm. They were not as easy to localize as the patch test reactions where the remnants of the adhesive mass clearly outlined the test area.

None of the 4 nontuberculous cases reacted to either test.

Of the 8 patients with active tuberculosis, all were positive to the patch test but only 2 showed reactions to the collodion test.

Of the 201 arrested cases, 183, or 91 per cent, showed a positive reaction to the patch test, and only 42, or 20.9 per cent, to the collodion test. These figures would have somewhat improved if the reactions had been read at the usual time, twenty-four hours later; they would not have materially changed, however, the great discrepancy between the positive reactions to either test. Erythema without induration occurred once as a reaction to the patch test but in 7 cases as a reaction to the collodion test. It is significant that 6 cases showed a skin reaction to the collodion control.

There were 141 reactors to the patch test with negative reactions to the collodion test, but not a single case was positive to the collodion test and negative to the patch test.

One reactor to collodion-tuberculin showed a contact reaction at a distant skin area as a result of contact with the test area during sleep.

DISCUSSION

These results indicate that the collodion method of applying tuberculin to the skin is far inferior to the patch test method. The figures obtained refer exclusively to the specific emulsion of tuberculin (Lederle, batch Nr. 61-1) in collodion used in this study. The method proved to be unsatisfactory and unreliable for tuberculin testing. Such emulsions can certainly be improved by a great number of variations, for example, of the concentration of tuberculin, of the proportion between tuberculin and the continuous phase of a dissolved plastic substance, the choice of plastic substance and its solvent and the con-

centration of the plastic substance in its solvents. Such changes and their combinations may result in a more useful test. Yet the inherent weaknesses of this method will probably remain the same as outlined in the beginning. There are too many variable factors to bring about uniform results. At least some of the plastics are slight skin irritants which may interfere with the interpretation of the reactions. The idea of a collodion-tuberculin test is promising. It remains to be seen whether the immanent disadvantages of this method can ever be overcome.

SUMMARY

To evaluate the comparative efficiency of the collodion-tuberculin test and the tuberculin patch test the same batch of tuberculin was used for both test methods.

In 213 well studied cases, most of whom had arrested tuberculosis, the patch test proved to be far superior to the collodion test.

The inherent weaknesses of the collodion test are outlined.

SUMARIO

A fin de justipreciar la eficacia comparativa de la prueba con la tuberculina-colodión y de la prueba del parche de tuberculina se utilizó el mismo lote de tuberculina con ambas técnicas.

En 213 casos estudiados a fondo, en la mayoría de tuberculosis estacionada, la prueba del parche resultó muy superior a la del colodión.

Señálanse las desventajas inherentes a la prueba del colodión.

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A MODIFIED TUBERCULIN PATCH TEST¹

THOMAS C. GRUBB

In 1937 Vollmer and Goldberger (1) described a patch test for detecting tuberculin sensitivity which consisted of a piece of filter paper impregnated with Old Tuberculin (concentration not stated) fastened to a strip of adhesive tape and applied to the subject's skin so that the filter paper came into direct contact with the skin. A control patch, impregnated with the medium in which the tubercle bacillus was cultured, is usually included on the adhesive strip to detect sensitivity to substances other than tuberculin itself and thus avoid false positive readings. The advantages originally claimed for this test, such as painless administration, saving of time, limited area of reaction, avoidance of infections, failure to elicit constitutional and focal reactions, etc., have apparently been substantiated because the test has become increasingly popular within recent years.

Dissatisfaction with the Vollmer and Goldberger test has recently been voiced by Grozin (2) who describes it as a "blind" test and notes the following disadvantages. If the patch is removed too soon, a positive reaction may be missed; or, if it is allowed to remain on the skin too long, severe local reactions and painful vesiculation may develop. Since various individuals differ greatly in their sensitivity to tuberculin, and since there is no way of knowing beforehand the sensitivity status of the subject, the objection of Grozin would appear well taken. If the patch is disturbed at various intervals to take a "peek" at the developing reaction in the hope of removing it before too severe a reaction develops, the effectiveness of the test is destroyed and a negative reaction may be recorded for a subject who is actually tuberculin-positive. Furthermore, there is some disagreement concerning the length of time the patch should be allowed to remain in place. Taylor (3) claims that three days is the minimum time while Neiman, Rosenthal and Motel (4) recommend four days. Palin (5) noted that in some cases positive tests did not appear until five to seven days after application of the patch.

To overcome these difficulties of the "blind" test, Grozin has devised a patch which contains small flaps cut in the adhesive strip above the tuberculin-impregnated filter paper disks. By lifting these flaps at occasional intervals, the progress of the reaction may be observed. However, this procedure obviously disturbs the continuous contact of the tuberculin with the skin and may invalidate the results, as described above. The purpose of this report is to describe another type of patch test which obviates the disadvantages of the "blind" test while retaining the advantages of the patch principle.

PREPARATION AND APPLICATION OF THE PATCH

A piece of heavy cellulose acetate film (photographic film with the emulsion and antihalation backing removed by washing in hot water is satisfactory) is

¹ From the Department of Bacteriology, University of Maryland, Baltimore, Maryland.

cut into squares of 0.8 cm. size. A drop (0.05 cc.) of undiluted Old Tuberculin² is placed in the centre of the square and allowed to evaporate to dryness. A strip of adhesive tape, approximately one and one-fourth inches long, is laid on a piece of cardboard (adhesive side up) and a circular hole is punched out of the centre with a cork borer having a diameter slightly smaller than 0.8 cm. The film is then placed over the hole in the adhesive strip with the tuberculin-coated side up. The patch may then be applied directly to the skin (figure 1); or, if it is not to be used immediately, the adhesive side may be covered with a strip of



FIG. 1 Adhesive tape with a "window" permitting observation of the reaction which develops beneath the tuberculin-coated film.

crinolin, such as used to cover "band-aids" or the commercial type of Vollmer patch test.

The patch is applied in the usual manner after cleansing the skin with ether or a similar solvent. It is essential that the coated film be placed in firm contact with the skin and allowed to remain in place for forty-eight hours, although it may be removed after shorter or longer intervals, depending upon the speed with which the reaction develops. The advantages of this test are manifest. The reaction may be observed through the transparent "window" during its entire

² The Old Tuberculin employed in these tests was supplied through the courtesy of the Sharp and Dohme and Lederle Companies.

progress without removal of the patch. The patch may be removed as soon as a definite positive test develops; thus there is little possibility of missing a positive reaction by too early removal, or the development of severe reactions by too prolonged contact. In case there is any doubt as to the presence of erythema at any time, it is only necessary to apply slight pressure to the "window" and, if active hyperemia is present, it fades immediately, whereas, if no reaction has occurred, pressure does not alter the color of the skin.

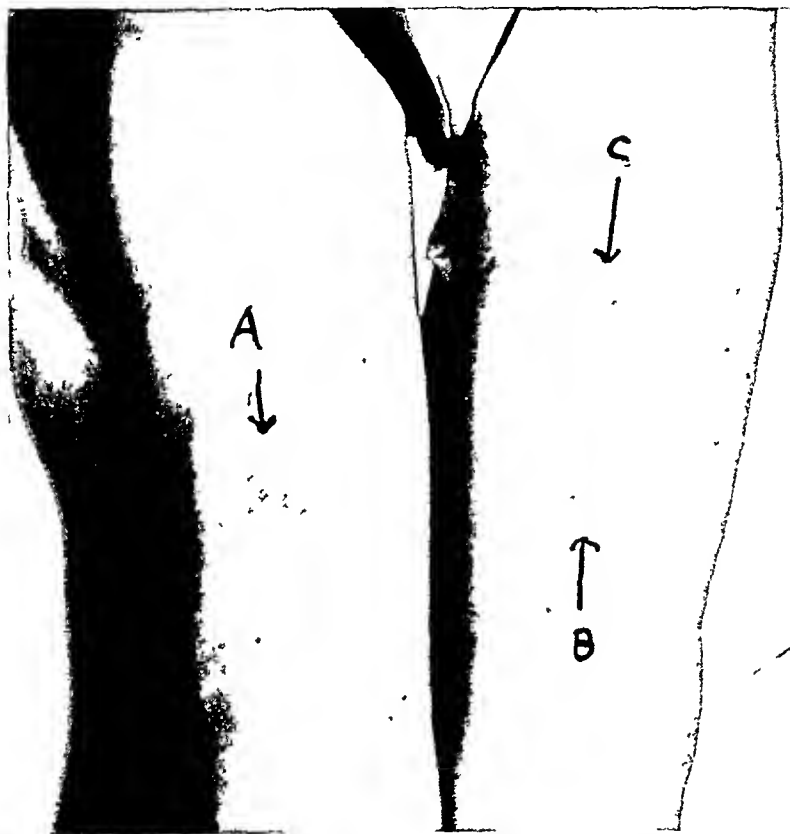


FIG. 2. Comparison of reactions produced by the Vollmer patch test (commercial) and the film test. A shows reaction caused by film test. B and C are reactions produced by Vollmer test. Note that B produced a much stronger reaction than C.

COMMENT

Vollmer claimed that impregnated and dried filter papers retained their potency indefinitely, and there is every reason to believe that tuberculin dried on the film will retain its potency for a similar period. Tuberculin diluted 1:1, 1:2 and 1:3 with distilled water produced progressively weaker reactions and experience indicates that it should not be diluted more than 1:1. The Vollmer patch test was compared with the "window" test on 30 students and in every instance the reactions of the stronger of the two Vollmer tests (on the same patch) and the film test containing undiluted tuberculin, when applied on the same subject, were of equal intensity (figure 2). While no reactions to the

film itself have thus far been observed, to detect this possibility, an uncoated, control patch might easily be included on the adhesive strip.

SUMMARY

A modified patch test is described which consists of a piece of transparent cellulose acetate (photographic) film containing a drop of dried, undiluted Old Tuberculin held in contact with the skin by means of a strip of adhesive tape. A circular hole in the tape provides a window through which the developing reaction may be observed at all times. Thus it is possible to avoid missing positive reactions by too early removal of the patch, and severe reactions may be prevented by removing the patch as soon as a definite positive reaction is observed.

SUMARIO

Descríbese una modificación de la prueba del parche, que consiste en usar un trozo de película (fotográfica) de acetato-celulosa transparente que contiene una gota de tuberculina antigua sin diluir, seca, mantenida en contacto con la piel por medio de una tira de esparadrapo. Un orificio circular en la tira facilita una ventana a través de la cual puede observarse constantemente las reacciones producidas, de manera que no se pasan por alto las reacciones positivas, debido a retirarse demasiado pronto el parche, y se impiden las reacciones graves retirándolo apenas se observe una reacción positiva bien definida.

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CLOROX DIGESTION¹

A Comparison of Clorox Digestion and Three Other Methods for Finding Acid-fast Organisms in Sputum

GEORGE M. CAMERON AND RUTH CASTLES

In a previous publication (1), a study was presented which brought out comparative values of the direct smear, the sodium hydroxide (2), autoclave and clorox (3) digestion procedures as a means of finding the tubercle bacilli in specimens of sputum.

At that time, results were reported on 211 specimens of sputum, of which 75 were positive. The advantages of the clorox method were demonstrated. The direct smears were prepared routinely in the laboratory and rechecked for comparison with the other three methods used on each specimen.

The present report includes the examination of 329 specimens. In this series the stained specimens studied were all prepared by the same individual in order to eliminate any personal factor which might be involved in such preparations.

A number of interesting facts have evolved from a comparison of the observations made by each of the four methods used. Due to the very satisfactory results which are being obtained in the Division of Laboratories of the Tennessee Department of Public Health, by using the clorox digestion procedure, this study is being presented.

This study of 329 specimens yielded 114 positives by one or more methods. In 19 of the 329, only one or two typical organisms were found, and new specimens were requested. The remaining 196 specimens were negative by all methods used.

Of the 114 specimens found positive by one or more methods, the total number found by each method was as follows:

Number of Positives by Each Method as Compared to the Total Positives Found

Method	Number Positive	Per Cent of Total Positive
Direct.....	71	62
Sodium hydroxide.....	90	79
Autoclave.....	95	83
Clorox.....	107	94
Total by one or more methods.....	114	100

A compilation of the number of organisms per microscopic field for the 114 positive specimens is presented in the following tabulation. This shows the number of specimens for each method which yielded a count not exceeded by any other method.

¹ From the Division of Laboratories, Tennessee Department of Public Health, Nashville, Tennessee.

Positive Specimens Yielding Highest Counts per Microscopic Field by Methods Indicated

Method	Number
Direct.....	5
Sodium hydroxide.....	9
Autoclave.....	10
Clorox.....	72
	<hr/>
Total.....	96
Autoclave, clorox and direct.....	1
Autoclave and direct.....	1
Sodium hydroxide and direct.....	1
Clorox and direct.....	2
Clorox, sodium hydroxide and autoclave.....	2
Clorox and autoclave.....	4
Clorox and sodium hydroxide.....	7
	<hr/>
Total.....	18*
	<hr/>
Grand Total.....	114

* Eighteen specimens yielded equivalent counts by two or more methods.

A study of the above listing shows that the number of organisms found per microscopic field by the clorox method in 88 of 114 positives, or 77 per cent of the specimens, was not exceeded by the findings for other methods. The sodium hydroxide method ranks second with 19 specimens, or 17 per cent; the autoclave method third with 18 specimens, or 16 per cent; and the direct smear ranks low with only 10 specimens, or 9 per cent of the positive specimens yielding counts of organisms per microscopic field not exceeded by any other method.

The number of positive specimens which were found positive by only one procedure is listed, by method, below:

Specimens Positive by Only One Procedure

Direct.....	1
Sodium hydroxide.....	1
Autoclave.....	5
Clorox.....	11

Again, it is evident that the clorox method has proved more effective for specimens containing very few organisms than any of the other three methods.

Out of the 114 specimens found positive by one or more of the methods used, one or more organisms were found by each method in 66 specimens, or in 58 per cent of the total specimens found positive.

In the following tabulation, the fields examined represent the number of microscopic fields necessary to examine to find the specimen positive by the method being used. For the 66 specimens found positive by all four methods, the total fields examined by each method were determined, together with the total number of organisms found in these fields. The average number of organ-

isms found by each method per 100 microscopic fields was computed from these figures. The results are tabulated below:

Average Organisms Found per 100 Microscopic Fields Computed from 66 Specimens Found Positive by All Methods Used

Method	Total Fields	Total Organisms Found	Organisms per 100 Fields
Direct.....	1,128	1,000	89
Sodium hydroxide.....	515	2,121	412
Autoclave.....	646	1,810	280
Clorox.....	424	4,940	1,165

Again, these figures show the efficiency of the clorox method for digestion of sputum and concentration of tubercle bacilli to have been considerably greater than for any of the other methods used in this study.

DISCUSSION

Out of the 114 specimens found positive in this study, 90 were sent in for diagnosis and 16 for check on treatment. The purpose of the remaining 8 specimens was not designated.

In analyzing the above observations, one point is outstanding. In every compilation of figures the clorox method has proved more efficient than the other methods used in this study. Together with this, one should consider the freedom of the microscopic field from visible extraneous materials by the clorox method as compared to the other methods. It should be remembered, however, that the clorox method is for finding organisms microscopically and not for animal inoculation and culture. Oliver and Reusser (3) state that tubercle bacilli are killed by this method.

SUMMARY

1. In this study the clorox digestion method of Oliver and Reusser proved to be more efficient in finding tubercle bacilli than did the other methods used.
2. The clorox digestion method yields a microscopic field in which no visible extraneous material interferes with finding tubercle bacilli.
3. The clorox method is highly satisfactory as a concentration method as an aid in diagnosing or checking treatment in patients with tuberculosis. It is of value in public health laboratories and smaller laboratories.

SUMARIO

1. En este estudio la técnica de digestión del clorox de Oliver y Reusser resultó ser más eficaz para descubrir los bacilos tuberculosos que las otras técnicas utilizadas.
2. La técnica de digestión del clorox obtiene un campo microscópico en el cual ninguna sustancia extraña visible impide descubrir los bacilos tuberculosos.
3. La técnica del clorox es sumamente satisfactoria para la concentración y para ayudar en el diagnóstico o la comprobación del tratamiento en los tuberculosos, siendo de valor en los laboratorios de sanidad y en los laboratorios pequeños.

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MEDICINE AS PRACTICED DURING THE 1840'S

A Comparison

WILLIAM DOSITE POSTELL¹

Recently, the Library of the Louisiana State University School of Medicine was the recipient of two interesting publications; one entitled *The Young Stethoscopist*, by Henry Ingersoll Bowditch, M.D. (1), the other *Consumptive Curable!*, by a Dr. Hall (2). These publications are interesting for the contrast they picture of medical practice during the 1840's. *The Young Stethoscopist* is scientific medicine, the Art as practiced by Hippocrates. *Consumption Curable!* depicts the other side of the story, that is, practice that smacks of quackery.

Dr. H. I. Bowditch (1808-1892), a resident of Massachusetts and a graduate of Harvard Medical School, was a pioneer specialist in diseases of the chest. Some of his works are rated as classics and have often been referred to in the literature. He was fortunate in having studied in Paris under Pierre Louis where he received excellent training in the principles of the examination of the chest by auscultation and percussion. Early in his career he wrote *The Young Stethoscopist*, a little book even now referred to as the best and most detailed description of early pulmonary tuberculosis that has ever appeared in America or any other country. Dr. Lawrason Brown, late Director of the Trudeau Sanatorium, speaks highly of this work. He states, "... it is so good that many textbooks today could better use it to replace their paragraphs upon this subject." (3, p 185)

A reviewer in the Buffalo Medical Journal (4) devoted ten pages to reviewing this book and his only criticism is its length. He felt that a publication of such merit should have treated its subject more fully.

It is only necessary to quote a few passages from this work to obtain a true estimate of its worth. As Doctor Bowditch stated in his preface (5, p. vii):

"In conclusion, while presenting this little work on the physical signs, let me disclaim all intention of placing them higher than they really deserve.... Amidst the niceties of our physical examinations we are apt to neglect the rational signs. The truth is, that he who scoffs at either must necessarily be a child in the diagnosis of not a few diseases; and he who cultivates both with the clear, keen-sighted eye of a true observer and then notes their mutual relations, is the truly wise physician."

After giving detailed instructions for the physical examination, Doctor Bowditch describes râles and their importance, as they always indicate disease, whether it is only a slight swelling of a bronchial membrane or the complete ulceration and destruction of an entire lobe of one lung. Then speaking of the condition of the lung when groups of tubercles are intermixed with the healthy tissue, he goes on to state (6, pp. 66-7):

¹ Librarian, Louisiana State University School of Medicine, New Orleans, Louisiana.

"When the lung is in this condition, if you cause the patient to cough, you will hear, at times, a single click or a single sonorous râle or whistle of the most delicate and distant character. Either of these sounds, heard ever so slightly, just below the clavicle, or at the top of the shoulder, (while in the remainder of the lung is heard healthy respiratory murmur), may be considered as a very unfavorable sign. If combined with any change in the inspiration or expiration, they become still more momentous. If with the above

CONSUMPTION
CURABLE!
THE
YOUNG STETHOSCOPIST,
OR THE
STUDENT'S AID
TO
AUSCULTATION.
CONSUMPTION:
BY DR. HALL,
OF
NEW ORLEANS
BOSTON:
WILLIAM D. TICKNOR & CO.,
NEW YORK:
J. & H. G. LANGLEY,
No. 8 Astor House.
1846.

FIG. 1

Fig. 1. Title page of *The Young Stethoscopist*

FIG. 2

Fig. 2. Title page of *Consumption Curable!*

signs there be a change on percussion; especially, if united with, the most trivial, rational symptoms of phthisis, you may be almost morally certain that tubercles have been developed . . ."

In regard to phthisis in children Doctor Bowditch had this to say (7, p. 76):

"... Phthisis in children rarely presents the same manifest and regularly ordered signs as are found in adults; and for the diagnosis we must depend chiefly on the rational signs."

In his description of this book, Doctor Brown concludes his account with this statement (8, p. 190): "It is questionable whether a better description of the methods of physical exploration in the diagnosis of early pulmonary tuberculosis has ever been written."

Now consider the other side of the picture as represented by *Consumption Curable!*, as written by Doctor Hall. Here one finds the practice of medicine reduced to quackery. This pamphlet was written for the gullible public and, although Doctor Hall tries to give the impression that he is discussing the subject "Consumption" within all the ethics of scientific medical practice, he probably fooled no one, unless it were those who were suffering from pulmonary tuberculosis. A search was made through the medical journals of that period to see if any mention was made of this pamphlet, but not a single reference could be found. It would almost seem as if Doctor Hall's claims were so ridiculous that no medical editor bothered to repudiate his statements.

Just who was Doctor Hall it was not possible to assert with any degree of assurance. The pamphlet does not give his full name or anything else concerning him, except that he was a resident of New Orleans from November 1 until May 1 of each year. There is no such pamphlet with this title listed in the Index Catalogue of the Library of the Surgeon-General's Office, but from other pamphlets with closely related titles one suspects that the author was Dr. William Whitty Hall (1810-1876), a graduate of Transylvania Medical College, who practiced medicine in the South for some fifteen years before moving to New York.

In the beginning of his pamphlet, Doctor Hall gives a general description of consumption for the public. His description is probably not far wrong, and it comes rather as a shock to reach that section entitled, "What do you do for consumption?" and find this introductory statement (9, p. 18):

"The most interesting reply, at least to the patient is—I cure it! Tubercles are absorbed, taken away or encysted. Large cavities are encased, small ones healed up. This is done in a manner not disagreeable, calomel, emetics, blisters, caustics, seatons and issues, not being used. It is accomplished by a method unknown to the world, until within a short time past, and the success which has attended the judicious employment of the means used, has been uniform, and encouraging, in the highest degree. Already there are men of high moral worth, all over the Union, who are prepared at any day or hour, when properly approached to bear a decided, and grateful testimony in its favor."

Doctor Hall then describes how simple and beneficial is his treatment. Most patients require only one or two visits to his office, although a few must make several visits over a period of some weeks. The remedies are applied at home among the pleasant surroundings of home and family. At this point he attempts to modify his first claims as to the curability of consumption by stating that not every case is curable, but four out of five persons can be cured who make a timely application.

He does not profess to cure any one who has been confined to his bed for any length of time or who is too weak to come to his office. However, he cites one

case where the patient had been confined to his bed for weeks and could not sit up more than one hour a day, with constant night sweats, but after seeing him but once he was able in two weeks to ride some eight or ten miles to pay him an office visit.

When it comes to divulging his remedy or treatment Doctor Hall has this to say (10, p. 23):

"It is not designed at present to communicate the means employed Let it, be distinctly noted, that I am any time, under proper circumstances, perfectly willing to communicate all I yet know, to any well educated young physician of genius, talent, of a towering ambition, who will give suitable guarantees, that he will devote his whole life, exclusively, to the mode of practice adopted by me, and to its improvement, in the treatment of this one disease" (11, p. 23).

Doctor Hall then cites a number of cases which he has treated and cured. A few examples are here given (12, pp. 34-8):

Case 1

"A tall young man aged 22. . . principal symptoms, fixed pain in the left breast, emaciation, weakness, a troublesome cough at night of many months duration. I did not see him after giving the prescriptions, but he called in two months to say that he felt, and believed himself to be perfectly well."

Case 2

"Tall, thin gentleman aged 38. Taken with a cough three years ago, which now excites nausea and vomiting, with morning expectoration, left side fallen in. Writes in two months, that he believes with a little longer attention to the remedies, 'my disease would be entirely removed.' And with the letter, sent me another patient. Saw him once only."

Case 6

"Married man, aged 26; pulse 95; confined to bed all the time; daily chill, irregular sleep, cough very troublesome, frequent night sweats, unable to sit up. Attacked with spitting of blood for two years before; repeated since. . . his case had been given up as utterly hopeless by several different physicians in succession. I prescribed for him. The next time I saw him, was on the 15th day; was walking about; in two weeks more, could walk a mile without much fatigue. . ."

There were several other cases cited including a number of letters from patients, all attesting to their cures. Doctor Hall did not forget his fees. The last two pages are devoted to his "Terms." He preferred to have it understood by his patients as to his rates so there would be no embarrassment on anyone's part. Twenty dollars was charged for the first visit, and in case of complications thirty dollars was due on the fifteenth day and fifty dollars on the thirtieth day. Doctor Hall stated he did not care to make house visits, but in the case of an emergency he would do so. His charges for these visits were five dollars for the first and two dollars for each subsequent one.

Doctor Hall concludes with this statement (13, p. 54):

"In conclusion—it will be a source of the purest pleasure to the author, if the foregoing pages shall be instrumental in restoring even a few of the unfortunate afflicted, to health and happiness, and to stations of honorable usefulness to our common country and the age we live in."

This then is somewhat an outline of two publications issued within two years of each other depicting the extremes to which medical practice ascended and descended during this period when so many advances were being made in America in the study of pulmonary tuberculosis.

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AMERICAN TRUDEAU SOCIETY

Tuberculosis Control in Hospitals¹

A Study Made by the Committee on Hospital Personnel²

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INTRODUCTION

The practice of X-raying the chests of all patients admitted to general hospitals has long been advocated as one of the best means of finding undiagnosed cases of tuberculosis. Unfortunately, however, this plan had not been adopted generally prior to World War II and the ensuing shortage of personnel has not been conducive to extension of the practice.

In order to be in a position to outline sound policies for the postwar development of the country's hospitals, the Committee on Hospital Personnel of the American Trudeau Society with the coöperation of the American Hospital Association initiated an inquiry covering tuberculosis case-finding activities among hospital patients and personnel. In November, 1943, questionnaires were sent to all hospitals in the United States which operated schools of nursing accredited by the State Board of Nurse Examiners. Of the 1,284 hospitals in this category all were general hospitals with the exception of 36 institutions for mental patients.

These questionnaires were sent out in an effort to ascertain which methods are being followed in order to control tuberculosis among hospital patients and personnel, as well as the frequency with which the various methods are practiced by the hospitals studied. A copy of the questionnaire which contained eight questions appears in the appendix to this report.

Of the 1,284 hospitals to which the questionnaires were sent, 934, or 73 per cent, replied. This remarkably high return demonstrates the very real interest which exists in the subject of tuberculosis as an occupational disease among hospital personnel.

According to table 1, more large hospitals than small ones answered the questionnaires; approximately half of the hospitals with fewer than 50 beds sent replies, while 94 per cent of the institutions with 1,000 or more beds responded to the inquiry.

Table 2 indicates that tax-supported hospitals responded more readily than did those operated by non-profit organizations, while the response from proprietary (private) hospitals was poorest.

Since 32 of the 46 hospitals with 1,000 or more beds are institutions for mental

¹ This report was prepared by Helen S. Canny, assistant statistician of the National Tuberculosis Association.

² This committee is now known as the Committee on Tuberculosis among Hospital Personnel.

patients, all but one of which are operated by the states, this factor tends to color the data concerning state hospitals as well as those with 1,000 or more beds.

TABLE 1

Number and percentage of hospitals which replied to questionnaires, classified by bed capacity of hospital

BED CAPACITY OF HOSPITAL	TOTAL HOSPITALS SENT QUESTIONNAIRES	HOSPITALS REPLYING TO QUESTIONNAIRES	
		Number	Per cent of total
All sizes.....	1,284	934	72.7
Fewer than 50 beds.....	38	20	52.6
50 but less than 100 beds.....	285	185	64.9
100 but less than 200 beds.....	500	363	72.6
200 but less than 300 beds.....	235	177	75.3
300 but less than 500 beds.....	119	94	79.0
500 but less than 1,000 beds.....	58	49	84.5
1,000 beds and over.....	49	46	93.9

TABLE 2

Number and percentage of hospitals which replied to questionnaires, classified by type of hospital

TYPE OF HOSPITAL	TOTAL HOSPITALS SENT QUESTIONNAIRES	HOSPITALS REPLYING TO QUESTIONNAIRES	
		Number	Per cent of total
All types.....	1,284	934	72.7
Public.....	176	142	80.7
Federal.....	3	2	1
State.....	69	61	88.4
City-county.....	104	79	76.0
Non-profit organization.....	1,035	757	73.1
Church.....	508	362	71.3
Other non-profit association.....	527	395	75.0
Proprietary.....	73	35	47.9

¹ Per cent not shown when base is less than 25.

ANALYSIS OF DATA

This report is based on the 934 hospitals with accredited schools of nursing which replied to questionnaires sent out late in 1943. Since these 934 hospitals comprise 73 per cent of the entire number which maintain such nursing schools, they must be considered as representative of the total group.

Bed capacity and type of control: One of the first items of interest concerning the hospitals included in this study is the relationship between bed capacity and the type of agency which operates the institution.

All of the 46 hospitals with 1,000 or more beds each are tax-supported and they represent one-third of all public hospitals which responded to the questionnaire. Half of the private hospitals maintain between 50 and 100 beds, while 44 per cent of the hospitals run by non-profit associations can accommodate between 100 and 200 patients each.

In other words, the public hospitals included in this study are for the most part very large institutions; those operated by non-profit organizations are of moderate size; and almost all the private hospitals are small.

TABLE 3
Hospitals of specified size, classified by type of hospital

TYPE OF HOSPITAL	HOSPITALS OF SPECIFIED SIZE														
	Total	Fewer than 50 beds		50 but less than 100 beds		100 but less than 200 beds		200 but less than 300 beds		300 but less than 500 beds		500 but less than 1,000 beds		1,000 beds and over	
		Number	Per cent of total	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total
All types.....	934	20	2.1	185	19.8	363	38.9	177	19.0	94	10.1	49	5.2	46	4.9
Public.....	142	2	1.4	13	9.2	23	16.2	12	8.5	22	15.5	24	16.9	46	32.4
Federal.....	2	—	—	—	—	—	—	—	—	2	1	—	—	—	—
State.....	61	1	1.6	2	3.3	9	14.8	4	6.6	5	8.2	6	9.8	34	55.7
City-county....	79	1	1.3	11	13.9	14	17.7	8	10.1	15	19.0	18	22.8	12	15.2
Non-profit organization...	757	14	1.8	154	20.3	330	43.6	162	21.4	72	9.5	25	3.3	—	—
Church.....	362	2	0.6	63	17.4	176	48.6	82	22.7	36	9.9	3	0.8	—	—
Other non-profit association.....	395	12	3.0	91	23.0	154	39.0	80	20.3	36	9.1	22	5.6	—	—
Proprietary.....	35	4	11.4	18	51.4	10	28.6	3	8.6	—	—	—	—	—	—

¹ Per cent not shown when base is less than 25.

This relationship between capacity and control of institutions affects the interpretation of the data throughout this survey. If, for example, the policy of X-raying employees is found to be related to the size of the hospitals, then it is likewise found to be related to the type of control.

The number of hospitals included in this study is unfortunately not large enough to establish significant relationships if the data are analyzed according to both size and type of control and, in addition, according to a third factor. Therefore, the reader must constantly keep in mind this interrelationship between the size and the type of control in those hospitals of the United States which are included in this study.

Admission of tuberculous patients: Almost one-third (29 per cent) of the 934

hospitals studied admit tuberculous patients, according to table 4; an additional 13 per cent admit them only in emergency, such as for diagnosis or for obstetrical care. Fifty-seven per cent of the hospitals never *knowingly* admit tuberculous patients, according to their statements, while the remaining one per cent failed to report their policies.

Table 4 also shows the relationship between the hospital's policy concerning the admission of tuberculous patients and the type of hospital. Far more public hospitals, whether operated by state, city or county, *knowingly* admit such

TABLE 4

Hospitals with specified policy as to the admission of tuberculous patients, classified by type of hospital

TYPE OF HOSPITAL	HOSPITALS WITH SPECIFIED POLICY AS TO ADMISSION								
	Total	Those which admit tuberculous patients		Those which admit tuberculous patients, emergency only ¹		Those which do not knowingly admit tuberculous patients ²		Those which did not report their policies	
		Number	Per cent of total	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total
All types.....	934	270	28.9	123	13.2	533	57.1	8	0.9
Public.....	142	88	62.0	12	8.5	41	28.9	1	0.7
Federal.....	2	2	³	—	—	—	—	—	—
State.....	61	39	63.9	8	13.1	13	21.3	1	1.6
City-county.....	79	47	59.5	4	5.1	28	35.4	—	—
Non-profit organization.....	757	174	23.0	108	14.3	468	61.8	7	0.9
Church.....	362	70	19.3	48	13.3	237	65.5	7	1.9
Other non-profit association.....	395	104	26.3	60	15.2	231	58.5	—	—
Proprietary.....	35	8	22.9	3	8.6	24	68.6	—	—

¹ Includes maternity cases and those for diagnosis only.

² Includes 16 hospitals which plan to do so after the war.

³ Per cent not shown when base is less than 25.

patients than do proprietary hospitals or those operated by non-profit associations. Five-eighths of the public hospitals admit tuberculous persons for treatment, compared to less than one-quarter of those maintained by non-profit organizations.

A direct correlation between the bed capacity of the hospital and the policy of admitting tuberculous patients is indicated in table 5. While only one-fifth of the hospitals having between 50 and 100 beds admit such patients, three-fourths of those with 500 to 1,000 beds and 94 per cent of those with 1,000 or more beds accept tuberculous persons for diagnosis and treatment.

Segregation of tuberculous patients: More than 90 per cent of the hospitals

which admit tuberculous persons segregate them from other patients. Among those hospitals which accept tuberculous patients in emergency only, the proportion which follows a policy of segregation is nearly as high.

TABLE 5

Hospitals which admit tuberculous patients, classified by bed capacity of the hospital

BED CAPACITY OF HOSPITAL	TOTAL HOSPITALS	HOSPITALS WHICH ADMIT TUBERCULOUS PATIENTS	
		Number	Per cent of total
All sizes.....	934	270	28.9
Fewer than 50 beds.....	20	3	1
50 but less than 100 beds.....	185	36	19.5
100 but less than 200 beds.....	363	79	21.8
200 but less than 300 beds.....	177	40	22.6
300 but less than 500 beds.....	94	33	35.1
500 but less than 1,000 beds.....	49	36	73.5
1,000 beds and over.....	46	43	93.5

¹ Per cent not shown when base is less than 25.

TABLE 6

Hospitals with specified policies as to segregation of tuberculous patients, classified by policy as to their admission

HOSPITAL POLICY REGARDING ADMISSION OF TUBERCULOUS PATIENTS	HOSPITALS WITH SPECIFIED POLICIES AS TO SEGREGATION						
	Total	Those which segregate tuberculous patients		Those which do not segregate tuberculous patients		Those which did not report policy as to segregation	
		Number	Per cent of total	Number	Per cent of total	Number	Per cent of total
All policies.....	934	604	64.7	91	9.7	239	25.6
Policy of admitting tuberculous patients.....	270	246	91.1	12	4.4	12	4.4
Policy of admitting tuberculous patients in emergency only.....	123	109	88.6	9	7.3	5	4.1
Policy of not <i>knowingly</i> admitting tuberculous patients.....	533	245	46.0	70	13.1	218	40.9
Policy regarding admission not reported.....	8	4	1	—	—	4	1

¹ Per cent not shown when base is less than 25.

Only 46 per cent of those hospitals which never *knowingly* admit tuberculous patients reported that the latter are segregated, while 41 per cent of the hospitals which refuse such patients admission failed to answer the inquiry with reference to segregation. The question may have appeared irrelevant to them.

The policy of segregating tuberculous patients varies directly with the size of the hospital, as shown in table 7. Fewer than 60 per cent of the smaller institutions segregate their tuberculous patients, whereas all but one of the hospitals with 1,000 beds and over segregate such patients. Again one must keep in mind the fact that 32 of these 46 large hospitals are institutions for mental patients.

TABLE 7

Hospitals which segregate tuberculous patients, classified by bed capacity of hospital

BED CAPACITY OF HOSPITAL	TOTAL HOSPITALS	HOSPITALS WHICH SEGREGATE TUBERCULOUS PATIENTS	
		Number	Per cent of total
All sizes.....	934	604	64.7
Fewer than 50 beds.....	20	8	1
50 but less than 100 beds.....	185	109	58.9
100 but less than 200 beds.....	363	216	59.5
200 but less than 300 beds.....	177	112	63.3
300 but less than 500 beds.....	94	71	75.5
500 but less than 1,000 beds.....	49	43	87.8
1,000 beds and over.....	46	45	97.8

¹ Per cent not shown when base is less than 25.

X-ray examinations of patients upon admission: Only 6 per cent of all hospitals included in this study take routine X-ray films of all patients upon admission,¹ according to table 8. Five per cent of the hospitals failed to reply to this question.

More than a third of the hospitals maintained by the states have adopted this routine practice, while but 3 per cent of the hospitals operated by non-profit organizations X-ray all patients upon admission. If all the tax-supported hospitals are considered as one group, then 23 per cent follow this progressive policy.

Hospitals which accept tuberculous patients for treatment are apparently more alive to the danger of admitting persons with undiagnosed tuberculosis than are those hospitals which do not *knowingly* admit tuberculous patients or which admit them in emergency only.

Sixteen per cent of the hospitals which accept such patients X-ray all of them upon admission, compared with but one per cent of those hospitals which refuse to admit them when their diagnosis is known. Personnel in the latter group of hospitals may be exposed to a greater hazard than are employees in those hospitals which knowingly care for patients with tuberculosis and who are therefore forewarned of the precautions they must take. Three per cent of the hospitals which admit tuberculous patients for surgery or for other emergency only, take routine X-ray films upon admission.

The proportion of active cases of tuberculosis found in X-ray surveys of consecutive admissions to general hospitals has in no case been less than 3 per 1,000 of the patients examined. By estimating on the basis of Doctor Plunkett's sug-

gestion,³ we find that approximately 40,000 patients with unrecognized active tuberculosis are admitted to hospitals annually. These patients constitute a reservoir of infection which threatens both hospital personnel and other patients. Certainly this fertile field for case-finding should not be neglected in view of the accessibility of the hospital population and the availability of necessary equip-

TABLE 8

Hospitals with specified policy as to the admission of tuberculous patients and number and percentage taking routine X-ray films upon admission, classified by type of hospital

TYPE OF HOSPITAL	ALL HOSPITALS			HOSPITALS WHICH ADMIT TUBERCULOUS PATIENTS			HOSPITALS WHICH ADMIT TUBERCULOUS PATIENTS IN EMERGENCIES ONLY ¹			HOSPITALS WHICH DO NOT <i>knowingly</i> ADMIT TUBERCULOUS PATIENTS ²			HOSPITALS WHICH DID NOT REPORT THEIR POLICY		
	Taking routine X-ray films upon admission			Taking routine X-ray films upon admission			Taking routine X-ray films upon admission			Taking routine X-ray films upon admission			Taking routine X-ray films upon admission		
	Total	Number	Per cent of total	Total	Number	Per cent of total	Total	Number	Per cent of total	Total	Number	Per cent of total	Total	Number	Per cent of total
All types.....	934	56	6.0	270	44	16.3	123	4	3.3	533	7	1.3	8	1	³
Public.....	142	32	22.5	88	29	33.0	12	1	³	41	1	2.4	1	1	³
Federal.....	2	—	—	2	—	—	—	—	—	—	—	—	—	—	—
State.....	61	23	37.7	39	20	51.3	8	1	³	13	1	³	1	1	³
City-county.....	79	9	11.4	47	9	19.1	4	—	—	28	—	—	—	—	—
Non-profit organization.....	757	22	2.9	174	13	7.5	108	3	2.8	468	6	1.3	7	—	—
Church.....	362	12	3.3	70	9	12.9	48	—	—	237	3	1.3	7	—	—
Other non-profit association.....	395	10	2.5	104	4	3.8	60	3	5.0	231	3	1.3	—	—	—
Proprietary.....	35	2	5.7	8	2	³	3	—	—	24	—	—	—	—	—

¹ Includes maternity cases and those for diagnosis only.

² Includes 16 hospitals which plan to do so after the war.

³ Per cent not shown when base is less than 25.

ment and personnel to take and interpret the X-ray films and to follow with clinical observation and other diagnostic procedures.

Preemployment X-ray films and subsequent X-ray films taken at regular intervals protect hospital personnel by discovering any cases of tuberculosis among their number while in the early stages of the disease. Radiological tests of this type likewise protect the patients from being infected by the employees.

³ Plunkett, R. E., and Mikol, E. X.: Unrecognized tuberculosis in general hospitals, *Am. Rev. Tuberc.*, 1940, 41, 381.

In order to protect hospital employees from being infected by patients, it is essential that X-ray films be taken routinely of all patients at the time they are admitted to our hospitals.

The 56 hospitals which systematically X-ray all patients at the time of admission are classified according to their size in table 9. From a study of this table it does not appear that a direct relationship exists between the size of the hospital and the policy of taking routine X-ray films at the time patients are admitted.

As we have previously pointed out, 70 per cent of the hospitals with 1,000 or more beds are mental institutions. Recent X-ray surveys of patients in mental hospitals have shown that a relatively high proportion of such patients have tuberculosis in some form. This factor, coupled with the overcrowding in such

TABLE 9

Hospitals which take routine X-ray films on admission, classified by bed capacity of hospital

BED CAPACITY OF HOSPITAL	TOTAL HOSPITALS	HOSPITALS WHICH TAKE ROUTINE X-RAYS FILMS ON ADMISSION	
		Number	Per cent of total
All sizes:	934	56	6.0
Fewer than 50 beds.....	20	—	—
50 but less than 100 beds.....	185	8	4.3
100 but less than 200 beds.....	363	10	2.8
200 but less than 300 beds.....	177	4	2.3
300 but less than 500 beds.....	94	2	2.1
500 but less than 1,000 beds.....	49	9	18.4
1,000 beds and over.....	46	23	50.0

institutions and the lack of coöperation on the part of many mental patients, tends to make the control of tuberculosis mandatory in hospitals for those mentally ill.

Tuberculin testing of hospital personnel: Approximately two-thirds of the hospitals included in this study follow the policy of tuberculin testing their student nurses, while but slightly more than one-fourth administer the test to graduate nurses.

This difference in policy is not surprising, since most nurses react positively to tuberculin by the time they have completed the usual training period of three years. In fact, mass tuberculin testing of graduate nurses might well be considered an uneconomical procedure.

Four per cent of the hospitals failed to reply to the inquiry covering the testing of student nurses, while 13 per cent did not respond to the question regarding the testing of graduate nurses.

Not quite one-fifth of the hospitals tuberculin test their resident physicians and only one-seventh test their other employees. One must not lose sight of the fact that 22 per cent of the institutions studied failed to reply to the former inquiry and 16 per cent to the latter.

Tuberculin testing of hospital personnel seems to have little or no relation to bed capacity, type of hospital or to the policy governing the admission of tuberculous patients.

Preemployment X-ray examinations of hospital personnel: During the past decade tuberculosis among nurses, especially among student nurses, has been the subject of extensive research. The data in tables 11, 12 and 13 testify to the fact that this wide-spread interest has had productive results.

Eighty-five per cent of all the hospitals included in this study X-ray their student nurses as a preemployment policy, while an additional one per cent X-ray the positive reactors to a routine tuberculin test.

TABLE 10

Hospitals which tuberculin test specified groups of employees on admission, classified by policy as to the admission of tuberculous patients

HOSPITAL POLICY REGARDING ADMISSION OF TUBERCULOUS PATIENTS	TOTAL HOSPITALS ¹	HOSPITALS WHICH TUBERCULIN TEST							
		Student nurses		Graduate nurses		Resident medi- cal staff		Other employees	
		Number	Per cent of total	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total
All policies.....	934	633	67.8	248	26.6	173	18.5	131	14.0
Policy of admitting tuber- culous patients.....	270	195	72.2	71	26.3	57	21.1	38	14.1
Policy of admitting tuber- culous patients in emer- gency only.....	123	83	67.5	37	30.1	23	18.7	20	16.3
Policy of not <i>knowingly</i> admitting tuberculous patients.....	533	350	65.7	139	26.1	91	17.1	72	13.5
Policy regarding admis- sion not reported.....	8	5	2	1	2	2	2	1	2

¹ Because some hospitals tuberculin test more than one group of their personnel, the total number of hospitals which tuberculin test all groups exceeds the total number of hospitals included in the study.

² Per cent not shown when base is less than 25.

So far as one can determine from the available data, the size of the hospital, its type of control and its policy concerning the admission of tuberculous patients seem to have little or no influence on the extent to which X-raying is employed at the time student nurses begin their training. Yet approximately three-fourths or more of all hospitals studied—whether large or small, publicly or privately operated and whatever their policy regarding the admission of tuberculous patients—do take preemployment X-ray films of their student nurses. Unfortunately the policy regarding other employees appears to be less progressive.

The emphasis placed on the high tuberculosis death rate among young women during the past twenty years has apparently influenced the thinking of hospital administrators to such an extent that they still fail to recognize tuberculosis as an equally serious problem among older adults.

Of those hospitals which admit tuberculous patients, a larger proportion X-ray their graduate nurses, resident medical staff and "other employees" prior to employment than do those hospitals which follow the policy of not admitting tuberculous patients *knowingly* or which admit them only in emergency.

Fewer than one-third of the hospitals studied (31 per cent) give their graduate nurses X-ray examinations at the time they are employed. Another one per cent X-ray the positive reactors to the tuberculin test; as a rule, positive reactors comprise an overwhelming majority of all graduate nurses. Thirteen per cent of the hospitals failed to report on the subject of giving preemployment X-ray examinations to graduate nurses.

TABLE 11

Hospitals which take preemployment X-ray films of specified employees, classified by policy as to the admission of tuberculous patients

HOSPITAL POLICY REGARDING ADMISSION OF TUBERCULOUS PATIENTS	TOTAL HOSPITALS ¹	HOSPITALS WHICH TAKE PREEMPLOYMENT X-RAY FILMS OF							
		Student nurses		Graduate nurses		Resident medi- cal staff		Other employees	
		Number	Per cent of total	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total
All policies.....	934	789	84.5	288	30.8	259	27.7	155	16.6
Policy of admitting tuber- culous patients.....	270	237	87.8	106	39.3	113	41.9	64	23.7
Policy of admitting tuber- culous patients in emer- gency only.....	123	108	87.8	30	24.4	31	25.2	14	11.4
Policy of not <i>knowingly</i> admitting tuberculous patients.....	533	438	82.2	149	28.0	112	21.0	76	14.3
Policy regarding admis- sion not reported.....	8	6	2	3	2	3	2	1	2

¹ Because some hospitals take preemployment X-ray films of more than one group of their personnel, the total number of hospitals which X-ray all groups exceeds the total number of hospitals included in the study.

² Per cent not shown when base is less than 25.

Only 28 per cent of the hospitals studied take preemployment X-ray films of their resident physicians and 17 per cent follow this policy with reference to other employees. Hospitals which failed to reply to this question concerning their resident medical staff numbered almost 23 per cent of the group studied, however, while 17 per cent gave no answer regarding preemployment X-ray films of their other employees.

A much greater proportion of the large hospitals give all their employees (other than student nurses) preemployment X-ray examinations than do the small hospitals. More than half the hospitals with 500 or more beds X-ray their graduate nurses and resident medical staff at the time they are employed, compared with fewer than 25 per cent of those hospitals which have fewer than 100 beds.

TABLE 12

Hospitals which take preemployment X-ray films of specified employees, classified by bed capacity of hospital

BED CAPACITY	TOTAL HOSPITALS ¹	HOSPITALS WHICH TAKE PREEMPLOYMENT X-RAY FILMS OF							
		Student nurses		Graduate nurses		Resident medical staff		Other employees	
		Number	Per cent of total	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total
All sizes.....	934	789	84.5	288	30.8	259	27.7	155	16.6
Fewer than 50 beds.....	20	13	2	5	2	2	2	1	2
50 but less than 100 beds..	185	138	74.6	41	22.2	16	8.6	25	13.5
100 but less than 200 beds..	363	308	84.8	89	24.5	68	18.7	37	10.2
200 but less than 300 beds..	177	160	90.4	57	32.2	64	36.2	25	14.1
300 but less than 500 beds..	94	86	91.5	39	41.5	51	54.3	20	21.3
500 but less than 1,000 beds.....	49	43	87.8	28	57.1	32	65.3	21	42.9
1,000 beds and over.....	46	41	89.1	29	63.0	26	56.5	26	56.5

¹ Because some hospitals take preemployment X-ray films of more than one group of their personnel, the total number of hospitals which X-ray all groups exceeds the total number of hospitals included in the study.

² Per cent not shown when base is less than 25.

TABLE 13

Hospitals which take preemployment X-ray films of specified employees, classified by type of hospital

TYPE OF HOSPITAL	TOTAL HOSPITALS ¹	HOSPITALS WHICH TAKE PREEMPLOYMENT X-RAY FILMS OF							
		Student nurses		Graduate nurses		Resident medical staff		Other employees	
		Number	Per cent of total	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total
All types.....	934	789	84.5	288	30.8	259	27.7	155	16.6
Public.....	142	119	83.8	62	43.7	64	45.1	48	33.8
Federal.....	2	2	2	1	2	1	2	1	2
State.....	61	46	75.4	30	49.2	26	42.6	25	41.0
City-county.....	79	71	89.9	31	39.2	37	46.8	22	27.8
Non-profit organization...	757	643	84.9	213	28.1	190	25.1	101	13.3
Church.....	362	299	82.6	78	21.5	66	18.2	28	7.7
Other non-profit association.....	395	344	87.1	135	34.2	124	31.4	73	18.5
Proprietary.....	35	27	77.1	13	37.1	5	14.3	6	17.1

¹ Because some hospitals take preemployment X-ray films of more than one group of their personnel, the total number of hospitals which X-ray all groups exceeds the total number of hospitals included in the study.

² Per cent not shown when base is less than 25.

A larger proportion of tax-supported hospitals X-ray their graduate nurses, resident medical staff and other employees when they are first engaged than do private institutions or those operated by non-profit associations. As before stated, however, hospitals of all types seem aware of the advantage of requiring student nurses to have preemployment X-ray examinations.

Periodic X-ray examinations of hospital personnel: Fifty-eight per cent of all hospitals which routinely make preemployment X-ray examinations of any group of their personnel also take periodic X-ray films of some group of employees later on. In almost all hospitals the student nurses represent the one group periodically X-rayed, just as they are by far the largest group to be given pre-employment X-ray examinations.

TABLE 14

Hospitals which take preemployment X-ray films¹ and which take periodic X-ray films of any group of employees, classified by policy as to the admission of tuberculous patients

HOSPITAL POLICY REGARDING ADMISSION OF TUBERCULOUS PATIENTS	HOSPITALS ¹ WHICH TAKE PREEMPLOYMENT X-RAY FILMS		
	Total	Those which take periodic X-ray films of any group of employees	
		Number	Per cent of total
All policies.....	797	460	57.7
Policy of admitting tuberculous patients....	238	164	68.9
Policy of admitting tuberculous patients in emergency only.....	108	64	59.3
Policy of not <i>knowingly</i> admitting tuber- culous patients.....	444	229	51.6
Policy regarding admission not reported....	7	3	²

¹ Includes all hospitals in which preemployment X-ray films are taken of at least one group of employees.

² Per cent not shown when base is less than 25.

A somewhat larger proportion of the hospitals which admit tuberculous patients take periodic X-ray films of some of their employees, compared with those hospitals which do not *knowingly* admit tuberculous patients or those which admit them for emergency treatment only.

Twenty-nine per cent of the hospitals which take preemployment X-ray films reported that they do not give any later X-ray examinations, while 8 per cent said that they take them "when indicated" or "when advised by the physician" and 5 per cent gave no report of their policy on this point.

Some relationship between the policy of taking periodic X-ray films and the type of hospital is shown in table 16. More public hospitals have adopted this practice than have proprietary institutions and those operated by non-profit organizations.

Three-quarters of the hospitals with 500 or more beds, which take preemployment X-ray films of any group of personnel, follow up these employees with one or more radiological examinations later on. Only half of the smaller hospitals

follow up their preemployment X-ray films with periodic chest examinations of this type at a later date.

Miniature X-ray films: The use of miniature X-ray films has apparently gained

TABLE 15

Hospitals which take preemployment X-ray films of any group of employees, classified by policy regarding periodic X-raying

HOSPITAL POLICY REGARDING PERIODIC X-RAYING	HOSPITALS ¹ WHICH TAKE PREEMPLOYMENT X-RAY FILMS OF ANY GROUP OF EMPLOYEES	
	Number	Per cent distribution
All policies.....	797	100.0
Policy of taking periodic X-ray films of any group of employees.....	460	57.7
Policy of taking later X-ray films "when indicated".....	66	8.3
Policy of not taking periodic X-ray films....	234	29.4
Policy as to periodic X-raying not reported.....	37	4.6

¹ Includes all hospitals which take preemployment X-ray films of at least one group of employees.

TABLE 16

Hospitals¹ which take preemployment X-ray films and which take periodic X-ray films of any group of employees, classified by type of hospital

TYPE OF HOSPITAL	HOSPITALS IN WHICH PREEMPLOYMENT X-RAY FILMS ARE TAKEN ¹		
	Total	Those which take periodic X-ray films of any group of employees	
		Number	Percent of total
All types.....	797	460	57.7
Public.....	119	84	70.6
Federal.....	2	1	²
State.....	46	33	71.7
City-county.....	71	50	70.4
Non-profit organization.....	651	359	55.1
Church.....	305	135	44.3
Other non-profit association.....	346	224	64.7
Proprietary.....	27	17	63.0

¹ Includes all hospitals in which preemployment X-ray films are taken of at least one group of employees.

² Per cent not shown when base is less than 25.

little popularity in general hospitals. Only 3 per cent of the 934 hospitals which participated in this survey use miniature X-ray equipment. The larger hospitals have found it more practical than the small hospitals; fewer than one per cent of hospitals with 50 to 100 beds have adopted this method, while 14 per cent of those with 500 to 1,000 beds and 15 per cent of those with 1,000 or more beds, use miniature X-ray equipment.

TABLE 17

Hospitals¹ which take preemployment X-ray films and which take periodic X-ray films of any group of employees, classified by size of hospital

BED CAPACITY OF HOSPITAL	HOSPITALS ¹ WHICH TAKE PREEMPLOYMENT X-RAY FILMS		
	Total	Those which take periodic X-ray films of any group of employees	
		Number	Per cent of total
All sizes	797	460	57.7
Fewer than 50 beds	13	7	2
50 but less than 100 beds	140	70	50.0
100 but less than 200 beds	310	163	52.6
200 but less than 300 beds	161	94	58.4
300 but less than 500 beds	88	59	67.0
500 but less than 1,000 beds	44	35	79.5
1,000 beds and over	41	32	78.0

¹ Includes all hospitals in which preemployment X-ray films are taken of at least one group of employees.

² Per cent not shown when base is less than 25.

TABLE 18

Hospitals which do not now tuberculin test student and graduate nurses, resident medical staff and other personnel, and those which plan to do so after the war emergency, classified by type of personnel

TYPE OF PERSONNEL	HOSPITALS WHICH DO NOT TUBERCULIN TEST CERTAIN GROUPS OF EMPLOYEES		
	Total	Those which plan to do so after the war emergency	
		Number	Per cent of total
Student nurses	251	11	4.4
Graduate nurses	554	39	7.0
Resident medical staff	505	29	5.7
Other employees	637	57	8.9

These findings in the larger hospitals were to be expected, in view of the fact that the chief advantages of such equipment are the speed with which many persons may be X-rayed and the convenience of the small films for filing. A hospital with fewer than 500 beds would rarely be faced with the problem of X-raying large numbers of patients or employees in a short period of time or with that of storing vast numbers of films in a limited space.

Postwar plans: Discouragingly few of the hospitals, which do not now practice the various techniques to protect their employees from tuberculosis, state that they plan to do so after the war emergency. Of the hospitals which do not tuberculin test the different groups of their personnel, between 4 and 9 per cent have postwar plans to administer the test.

TABLE 19

Hospitals which do not now take preemployment X-ray films of student and graduate nurses, resident medical staff and other personnel and those which plan to do so after the war emergency, classified by type of personnel

TYPE OF PERSONNEL	HOSPITALS WHICH DO NOT TAKE PREEMPLOYMENT X-RAY FILMS OF CERTAIN GROUPS OF EMPLOYEES		
	Total	Those which plan to do so after the war emergency	
		Number	Per cent of total
Student nurses.....	109	6	5.5
Graduate nurses.....	503	48	9.5
Resident medical staff.....	406	37	9.1
Other employees.....	589	69	11.7

TABLE 20

Hospitals which do not take routine X-ray films of patients on admission, and those which plan to do so after the war emergency, classified by type of hospital

TYPE OF HOSPITAL	HOSPITALS WHICH DO NOT TAKE ROUTINE X-RAY FILMS OF PATIENTS ON ADMISSION		
	Total	Those which plan to do so after the war emergency	
		Number	Per cent of total
All types.....	834	27	3.2
Public.....	99	9	9.1
Federal.....	2	—	—
State.....	34	5	14.7
City-county.....	63	4	6.3
Non-profit organization.....	703	18	2.6
Church.....	326	4	1.2
Other non-profit association.....	377	14	3.7
Proprietary.....	32	—	—

Similarly, only a small proportion of those hospitals which do not now take preemployment X-ray films of their employees have made plans to follow this policy when the war emergency has ended.

Of the 834 hospitals which reported that they do not X-ray patients routinely on admission, only 3 per cent plan to do so after the war emergency. A compari-

son of hospitals by type of control indicates that a larger proportion of public hospitals which do not now X-ray their patients plan to carry out this progressive practice as soon as the war is over.

Private hospitals and those operated by non-profit associations use routine tuberculin tests and X-ray films as a control measure less frequently than do public hospitals, and fewer of the first two groups have postwar plans to adopt these practices.

SUMMARY

The Committee on Hospital Personnel of the American Trudeau Society sent out questionnaires to the 1,284 general and mental⁴ hospitals in the United States which maintain accredited nursing schools. As a result of this inquiry replies were received from 934 hospitals, or nearly three-fourths of the total number. The survey was planned to ascertain what methods are being used by these hospitals to control tuberculosis among hospital patients and personnel.

About two-thirds of the 934 hospitals tuberculin test their student nurses, while an even larger proportion, 85 per cent, X-ray this group. Preemployment X-ray examinations were used more frequently than tuberculin tests in the case of each group of employees. Yet, only 31 per cent of the 934 hospitals studied X-ray their graduate nurses, 28 per cent their resident medical staff and 17 per cent their other employees.

Only 58 per cent of the hospitals which take preemployment X-ray films of some or all of their personnel follow up this practice with routine periodic X-raying of their employees. A much greater proportion of the large hospitals and of tax-supported institutions take routine periodic X-ray films of their personnel than do the smaller hospitals and those operated privately or by non-profit organizations.

The fact that only 6 per cent of the 934 hospitals included in the study X-ray all patients upon admission indicates the hazard of infection from patients with undiagnosed tuberculosis to which hospital personnel are exposed. Public hospitals exercise this control measure much more extensively than do semi-private and private institutions.

Sixteen per cent of the hospitals which accept tuberculous patients X-ray all their patients on admission, while only one per cent of the 533 hospitals which never *knowingly* admit tuberculous patients have adopted this practice. Moreover, only 3 per cent of all hospitals studied which do not now X-ray their patients on admission plan to do so after the war emergency.

Apparently the war cannot serve as an excuse for the failure of hospitals to protect their employees from tuberculosis. Lack of postwar plans to X-ray patients and personnel indicates the need for an educational campaign among hospital administrators and boards of directors. Certainly tuberculosis case-finding among the patients and personnel of general hospitals should be much more widely practiced throughout the country.

⁴ Of the hospitals sent questionnaires, 36 were institutions for mental patients.

SUMARIO

Con el propósito de averiguar qué métodos se utilizaban para combatir la tuberculosis entre enfermos y empleados, la Comisión de Personal Hospitalario de la American Trudeau Society distribuyó cuestionarios entre los 1,284 hospitales generales y nosocomios⁵ de los Estados Unidos que mantienen escuelas de enfermería reconocidas. Respuestas al cuestionario fueron recibidas de 934 hospitales o sea tres cuartas partes del total.

Aproximadamente dos terceras partes de los 934 hospitales comprueban con tuberculina a las estudiantes de enfermería y una proporción aun mayor (85%) las radiografían. En lo tocante a los candidatos a empleo las radiografías son utilizadas más a menudo que las pruebas con tuberculina. Sin embargo, sólo 31% de los 934 hospitales radiografían a las enfermeras recibidas, 28% a los médicos residentes, y 17% a los demás empleados.

Sólo 58% de los hospitales que toman radiografías antes del empleo de parte del personal o de todo el mismo, siguen esa práctica con radiografías periódicas y sistemáticas de los empleados. Comparados con los hospitales más pequeños o administrados particularmente o por organismos filantrópicos, es mucho mayor la proporción de los hospitales grandes y las instituciones subvencionadas del erario público que radiografían periódicamente a su personal.

El hecho de que sólo 6% de los 934 hospitales comprendidos en el estudio radiografien a todos los enfermos a su ingreso indica el peligro que corre el personal hospitalario de contraer la infección, presente en enfermos que padecen de tuberculosis no diagnosticada. Los hospitales públicos utilizan ese método profiláctico mucho más que las instituciones semiprivadas y privadas.

Un 16% de los hospitales que aceptan tuberculosos radiografían a todos los enfermos a su ingreso, comparado con sólo 1% entre los 533 hospitales que jamás reciben *a sabiendas* tuberculosos. Además, sólo 3% de todos los hospitales estudiados que no radiografían hoy día a sus enfermos al ingreso, se proponen hacerlo después de terminada la guerra.

Aparentemente la guerra no puede servir de disculpa a los hospitales para no proteger a sus empleados contra la tuberculosis. La falta de planes post-guerra para radiografiar a los enfermos y al personal indica la necesidad de llevar a cabo una campaña educativa entre los administradores y juntas directivas de los hospitales. No cabe duda de que el descubrimiento de casos entre los enfermos y el personal de los hospitales generales debe ser mucho más impulsado en todo el país.

⁵ De los hospitales que recibieron cuestionarios 36 eran instituciones dedicadas a casos mentales.

APPENDIX

Questionnaire Sent to 1,284 Hospitals

Mr. George Bugbee, secretary of the American Hospital Association, and Dr. David Cooper, chairman of the A. H. A. tuberculosis section, join us in asking you to check the following questions on tuberculosis case finding among hospital personnel and patients. Please check each inquiry and return this form in the inclosed envelope. A copy of the committee report will be sent to each superintendent who returns this questionnaire. Your comments are invited; please use the back of this form. Thank you.

LEOPOLD BRAHDY, M. D.

Chairman, Committee on Hospital Personnel,
American Trudeau Society

	Yes	No	If "No", but you plan to do so after the war emergency, check below
<i>Patients</i>			
1. Do you knowingly admit tuberculosis patients?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Do you segregate tuberculosis patients?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you a separate ward or section for them?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Do you take routine chest X-rays of all admissions?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Do you use any other routine case-finding method?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If yes, please specify.....			
.....			
<i>Employees</i>			
5. Do you do tuberculin tests on employees?.....			
Student nurses.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Graduate nurses.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Resident medical staff.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other employees.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Do you take pre-employment X-rays of hospital employees?			
Student nurses.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Graduate nurses.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Resident medical staff.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other employees.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Do you take later or periodic chest X-rays of employees?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Miniature X-rays</i>			
8. Do you use miniature X-ray method for any of these examinations?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If yes, please state what method is used.....			
.....			
.....			

AMERICAN TRUDEAU SOCIETY

Notice

Due to an error in office records, the name of Dr. Charles R. Reynolds, of Chicago, Illinois, appeared in the list of the deceased members of the American Trudeau Society, published on page 266 in the September, 1945 issue of the *AMERICAN REVIEW OF TUBERCULOSIS*. It is a pleasure to report to General Reynolds' many friends in tuberculosis control work that notice of his death was, as Mark Twain put it, "premature" and that he is actively at work with the American College of Physicians.

INDEX OF SUBJECTS AND AUTHORS

- Acid-fast bacilli in nontuberculous pulmonary disease, 36
- Adult, Protracted primary tuberculosis in the, with some observations on "lymphoglandular-endogenous reinfection (Ghon)," 312
- Adults, progressive- primary pulmonary tuberculosis in, Additional observations on, 155
- ALLEN, I. V., AND KELLY, C. W. End results of artificial pneumothorax, 495
- AMERICAN TRUDEAU SOCIETY:
 Officers, Executive Committee, Council Members and Advisory Board, 1945-1946, 175
 Report of the Committee on Rehabilitation, 176
 Deaths of Members, 266
 Report of the Committee on Tuberculosis in Industry, 351
 Report of the Committee on X-ray Apparatus and Technique, 352
 Report of the Committee on Postgraduate Medical Education, 440
 Report of the Committee on Evaluation of Laboratory Procedures, 442
 Report of the Committee on Medical Program, 443
 Report of the California Trudeau Society, 444
 Report of the Minnesota Trudeau Medical Society, 445
 Report of the Illinois Trudeau Society, 447
 Tuberculosis Control in Hospitals. A Study Made by the Committee on Hospital Personnel, 539
- Anatomical studies on human tuberculosis, XVIII. Additional observations on progressive primary pulmonary tuberculosis in adults, 155
- XIX. Protracted primary tuberculosis in the adult, with some observations on "lymphoglandular-endogenous reinfection (Ghon)," 312
- XX. Disseminated calcified small nodular hematogenous pulmonary tubercles, incidentally discovered, 505
- ANDERSON, NORMAN LARUE, AND WINN, WILLIAM DOUGLAS. Pneumoperitoneum and diaphragmatic paralysis, 380
- ANDOSCA, JOHN B., AND FOLEY, JOHN A. Pleural shock and cerebral embolism, 221
- Artificial pneumothorax, 21
 — — —, End results of, 495
- Aspiration, cavity, (Monaldi), Suction cabinet for use in, 502
- Associates, household, Tuberculosis in, 89
- Bacilli, Acid-fast, in nontuberculous pulmonary disease, 36
- BARACH, ALVAN L. Immobilization of both lungs, 122
- BASS, H. E., AND THOMPSON, G. D. CARLYLE. Incidence of tuberculosis in Japanese-Americans, 46
- Bed rest in tuberculosis, 15
 — — —, Strict, in pulmonary tuberculosis, 483
- BERG, WILLIAM N. Blood cell counts, 179
- BIRKELO, C. C. Discussion: Transient focal pulmonary edema, 1
- Blood cell counts, 179
- BOGEN, EMIL, AND STRICKLAND, G. H. Tuberculosis in a tropical naval hospital, 490
- BOOKS:
 BARACH, ALVAN L. Principles and practices of inhalational therapy, 169
 BAUER, JULIUS. Constitution and disease: Applied constitutional pathology, 173
 BRIEGER, E. M. The Papworth families: A 25 year survey, 166
 CAVINS, HAROLD M. National health agencies: A survey with especial reference to voluntary associations, 173
 CLAR, KATHLEEN C., HART, P. D'ARCY, KERLEY, PETER, AND THOMPSON, BRIAN C. Mass miniature radiography of civilians: For the detection of pulmonary tuberculosis, 173
 DESPAIGNE, DEMETRIO E. La lucha contra la tuberculosis en Cuba, 173
 GINES, ANGEL R. El sindrome humoral en la tuberculosis pulmonar, 173
 GOETZL, ALFRED, AND REYNOLDS, RALPH ARTHUR. Julius Tandler: A biography, 173
 HILLEBOE, HERMAN E., AND MORGAN, RUSSELL H. Mass radiography of the chest, 164

- JOAQUIN REY, AMADEO, CÉSAR PANGAS, JULIO, AND JORGE MASSÉ, RAUL. *Tra-tado de tisiología*, 173
- MUSTARD, HARRY S. *An introduction to public health*, 169
- OSBORNE, STAFFORD L., AND HOLMQUEST, HAROLD J. *Technic of electrotherapy: And its physical and physiological basis*, 170
- PIAGGIO, ARISTEO A., AND EPIFANIO, CLEOPATRA. *Significado económico de la morbilidad y mortalidad tuberculosas: Ensayo de estudio de sus valores para el Uruguay*, 173
- PUFFER, RUTH RICE. *Familial susceptibility to tuberculosis: Its importance as a public health problem*, 173
- RIST, EDOUARD. *Les symptomes de la tuberculose pulmonaire: Clinique, physiologic pathologique, thérapeutique*, 165
- SOTO BLANCO, JUAN. *Diagnóstico topográfico de los procesos pleuropulmonares: Estudio anatómico, clinico y radiológico*, 173
- STERN, RUDOLF A. *Trauma in internal diseases: With consideration of experimental pathology and medicolegal aspects*, 171
- TRAIL, R. R., TRENCHARD, H. J., AND KENNEDY, J. A. *Mass miniature radiography: A practical handbook*, 164
- Boletín de la Dirección General de Salubridad: Año 1943, 174
- Family health service in tuberculosis: Family health series guide for public health nurses No. 3A, 174
- Libro de oro: Dedicated to Alejandro A. Raimondi, 174
- Primera Conferencia Nacional de Tuberculosis: Realizada en Lima, del 12 al 17 de Octubre de 1942, 174
- Proteins and amino acids: Physiology, pathology, therapeutics, 174
- Publicaciones del Centro de Investigaciones Tisiológicas: Volumen VII, 174
- Report of the Committee on Reorganization of the Tuberculosis Service: Approved and ordered to be published by the Joint Tuberculosis Council, September 16, 1944, 174
- Studies of burns and scalds: (Report of the Burns Unit, Royal Infirmary, Glasgow, 1942-43), 174
- Tisiología, 174
- Tuberculosis in the United States. Graphic presentation. Volume 2. Proportionate mortality statistics for states and geographic divisions by age, sex, and race, 172
- Tuberculosis laws, rules, regulations, Florida: Arranged by topic, May, 1944, 174
- BRAY, HARRY A. *Strict bed rest in pulmonary tuberculosis*, 483
- Bronchography in pulmonary tuberculosis, V. Artificial pneumothorax, 21
- VI. Thoracoplasty, Part 1, 145
Part 2, 258
- Calcified small nodular hematogenous pulmonary tubercles, Disseminated, incidentally discovered, 505
- CAMERON, GEORGE M., AND CASTLES, RUTH. *Clorox digestion*, 530
- CASTLES, RUTH, AND CAMERON, GEORGE M. *Clorox digestion*, 530
- Cavity aspiration (Monaldi), Suction cabinet for use in, 502
- Cerebral embolism, Pleural shock and, 221
- Chemotherapy in experimental tuberculosis, 73
- of sulfones and sulfonamides in experimental tuberculosis, 304
- Children, Tuberculosis in, 392
- CLARKE, ROBERT W. *Degree of tuberculin sensitivity*, 424
- Clorox digestion, 530
- Collodion-tuberculin-test, Comparison of the tuberculin patch test and the, 521
- CORY, RICHARD A. S. *Acid-fast bacilli in nontuberculous pulmonary disease*, 36
- Counts, Blood cell, 179
- CROW, HORACE E., AND WHELCHER, FRED C. *Diaphragmatic paralysis and pneumoperitoneum*, 367
- CRUTCHLOW, EVERETT F. See PEIRCE, CARLETON B., *et al.*, 1
- CUTTING, WINDSOR C., GEBHARDT, L. P., PROESCHER, F., AND DURRUM, E. *Chemotherapy in experimental tuberculosis*, 73
- Cytotoxic action, Specific, of tuberculin, 65
- DAHLSTROM, A. W., AND MCGIBONY, J. R. *Tuberculosis among Montana Indians*, 104

- DAYMAN, HOWARD. Silicosis, 449
 Diaphragmatic paralysis and pneumo-peritoneum, 367
 ———, Pneumoperitoneum and, 380
 Diasone, Treatment of pulmonary tuberculosis with, 474
 Digestion, Clorox, 530
 Disease, Poncet's, 463
 ———, pulmonary, nontuberculous, Acid-fast bacilli in, 36
 Disseminated calcified small nodular hematogenous pulmonary tubercles, incidentally discovered, 505
 DORMER, B. A., FRIEDLANDER, J., AND WILES, F. J. Bronchography in pulmonary tuberculosis,
 V. Artificial pneumothorax, 21
 VI. Thoracoplasty,
 Part 1, 145
 Part 2, 258
 DURRUM, E. See CUTTING, WINDSOR C., *et al.*, 73
- Edema, pulmonary, focal, Transient, 1
 Embolism, cerebral, Pleural shock and, 221
 "Endogenous, lymphoglandular, reinfection (Ghon)," Protracted primary tuberculosis in the adult, with some observations on, 312
 Enzymes as factors in resistance to tuberculosis, 58
 Eosinophilia in silicosis, 337
 Epidemiology of tuberculosis in a mental hospital, 248
 Experimental tuberculosis, Chemotherapy in, 73
 ———, ——— of sulfones and sulfonamides in, 304
 ———, Streptomycin in, 269, 432
 ———, Streptothricin in, 299
 ———, Sulfadiazine in, 83
- Family histories in tuberculosis, 231
 FELDMAN, WILLIAM H., AND HINSHAW, H. CORWIN. Streptothricin in experimental tuberculosis, 299
 ———, ———, HINSHAW, H. CORWIN, AND MANN, FRANK C. Streptomycin in experimental tuberculosis, 269
 ———, ———. See HEILMAN, DOROTHY H., *et al.*, 65
 FERKANAY, JOSEPH E., AND LEE, RICHARD K. C. Tuberculosis survey of food handlers on the Island of Oahu, 51
 Focal pulmonary edema, Transient, 1
- FOLEY, JOHN A., AND ANDOSCA, JOHN B. Pleural shock and cerebral embolism, 221
 Food handlers on the Island of Oahu, Tuberculosis survey of, 51
 Founders of the National Tuberculosis Association, 345
 FRIEDLANDER, J. See DORMER, B. A., *et al.*, 21, 145, 258
 GASS, R. S. See PUFFER, RUTH R., *et al.*, 89
 GEBHARDT, L. P. See CUTTING, WINDSOR C., *et al.*, 73
 GERSTL, BRUNO, TENNANT, ROBERT, AND PELZMAN, OSCAR. Enzymes as factors in resistance to tuberculosis, 58
 GRUBB, THOMAS C. A modified tuberculin patch test, 526
- HABEEB, WILLIAM J. Eosinophilia in silicosis, 337
 HEILMAN, DOROTHY H., FELDMAN, WILLIAM H., AND MANN, FRANK C. The specific cytotoxic action of tuberculin, 65
 Hematogenous pulmonary tubercles, Disseminated calcified small nodular, incidentally discovered, 505
 HENDERSON, ARTHUR T. See PEIRCE, CARLETON B., *et al.*, 1
 HINSHAW, H. CORWIN, AND FELDMAN, WILLIAM H. Streptothricin in experimental tuberculosis, 299
 ———, ———. See FELDMAN, WILLIAM H., *et al.*, 269
 Histories, Family, in tuberculosis, 231
 Hospital, mental, Epidemiology of tuberculosis in a, 248
 ———, tropical naval, Tuberculosis in a, 490
 Household associates, Tuberculosis in, 89
 Human tuberculosis, Anatomical studies on,
 XVIII. Additional observations on progressive primary pulmonary tuberculosis in adults, 155
 XIX. Protracted primary tuberculosis in the adult, with some observations on "lymphoglandular-endogenous reinfection (Ghon)," 312
 XX. Disseminated calcified small nodular hematogenous pulmonary tubercles, incidentally discovered, 505
- Immobilization of both lungs, 122
 Incidence of tuberculosis in Japanese-Americans, 46

- Indians, Montana, Tuberculosis among, 104
- Indications for intrapleural pneumonolysis, 355
- Intrapleural pneumonolysis, Indications for, 355
- Japanese-Americans, Incidence of tuberculosis in, 46
- JONES, H. AUBREY. Indications for intrapleural pneumonolysis, 355
- KELLY, C. W., AND ALLEN, I. V. End results of artificial pneumothorax, 495
- LEE, RICHARD K. C., AND FERKANAY, JOSEPH E. Tuberculosis survey of food handlers on the Island of Oahu, 51
- Lungs, both, Immobilization of, 122
- "Lymphoglandular-endogenous reinfection (Ghon)," Protracted primary tuberculosis in the adult, with some observations on, 312
- MANN, FRANK C. See FELDMAN, WILLIAM H., *et al.*, 269
- , ———. See HEILMAN, DOROTHY H., *et al.*, 65
- MCCARTER, JOHN C., AND YOUMANS, GUY P. Streptomycin in experimental tuberculosis, 432
- MCCLOSKEY, W. T., AND SMITH, M. I. Chemotherapy of sulfones and sulfonamides in experimental tuberculosis, 304
- MCGIBONY, J. R., AND DAHLSTROM, A. W. Tuberculosis among Montana Indians, 104
- McKAY, JOSEPH W. See PEIRCE, CARLETON B., *et al.*, 1
- Medicine as practiced during the 1840's, 534
- Mental hospital, Epidemiology of tuberculosis in a, 248
- (Monaldi), cavity aspiration, Suction cabinet for use in, 502
- Montana Indians, Tuberculosis among, 104
- National Tuberculosis Association, Founders of the, 345
- Nodular hematogenous pulmonary tubercles, small, calcified, Disseminated, incidentally discovered, 505
- Nontuberculous pulmonary disease, Acid-fast bacilli in, 36
- Oahu, Island of, Tuberculosis survey of food handlers on the, 51
- OBITUARY: Sampson, Homer L., 1880-1945, 264
- OECHSLI, FRANK W., AND SMITH, C. RICHARD. Sulfadiazine in experimental tuberculosis, 83
- OLSON, KENNETH B., THOMPSON, JENCE F., AND ZINTHEO, CLARENCE J., JR. Treatment of pulmonary tuberculosis with diasone, 474
- Paralysis, Diaphragmatic, and pneumoperitoneum, 367
- , ———, Pneumoperitoneum and, 380
- Patch test, tuberculin, and the collodion-tuberculin test, Comparison of the, 521
- , ———, Modified, 526
- PATERSON, ROBERT G. Founders of the National Tuberculosis Association, 345
- PECK, WILLIAM M., AND WILLIS, HENRY STUART. Bed rest in tuberculosis, 15
- PEIRCE, CARLETON B., CRUTCHLOW, EVERETT F., HENDERSON, ARTHUR T., AND McKAY, JOSEPH W. Transient focal pulmonary edema, 1
- PELZMAN, OSCAR. See GERSTL, BRUNO, *et al.*, 58
- Pleural shock and cerebral embolism, 221
- Pneumonolysis, intrapleural, Indications for, 355
- Pneumoperitoneum and diaphragmatic paralysis, 380
- , Diaphragmatic paralysis and, 367
- Pneumothorax, Artificial, 21
- , ———, End results of, 495
- Poncet's disease, 463
- POSTELL, WILLIAM DOSITE. Medicine as practiced during the 1840's, 534
- Primary pulmonary tuberculosis, progressive, in adults, Additional observations on, 155
- tuberculosis, Protracted, in the adult, with some observations on "lymphoglandular-endogenous reinfection (Ghon)," 312
- PROESCHER, F. See CUTTING, WINDSOR C., *et al.*, 73
- Progressive primary pulmonary tuberculosis in adults, Additional observations on, 155

- Protracted primary tuberculosis in the adult, with some observations on "lymphoglandular-endogenous reinfection (Ghon)," 312
- PUFFER, RUTH R., STEWART, H. C., AND GASS, R. S. Tuberculosis in household associates, 89
- Pulmonary disease, nontuberculous, Acid-fast bacilli in, 36
- edema, focal, Transient, 1
- tubercles, hematogenous, Disseminated calcified small nodular, incidentally discovered, 505
- tuberculosis, Bronchography in, V. Artificial pneumothorax, 21 VI. Thoracoplasty, Part 1, 145 Part 2, 258
- —, primary, progressive, in adults, Additional observations on, 155
- —, Strict bed rest in, 483
- —, Treatment of, with diasone, 474
- "Reinfection (Ghon), lymphoglandular-endogenous," Protracted primary tuberculosis in the adult, with some observations on, 312
- Resistance to tuberculosis, Enzymes as factors in, 58
- Rest, Bed, in tuberculosis, 15
- , —, Strict, in pulmonary tuberculosis, 483
- Results, End, of artificial pneumothorax, 495
- RUSKIN, DAVE B. Epidemiology of tuberculosis in a mental hospital, 248
- Sampson, Homer L., 1880-1945, in memoir, 264
- SCHWARZ, J. Tuberculosis in children, 392
- SELIGSON, FRANK. Poncet's disease, 463
- Sensitivity, tuberculin, Degree of, 424
- Shock, Pleural, and cerebral embolism, 221
- Silicosis, 449
- , Eosinophilia in, 337
- SIMPSON, S. E. Family histories in tuberculosis, 231
- SINGER, PAUL, SOTTILARO, JOSEPH J., AND VOLLMER, HERMANN. A comparison of the tuberculin patch test and the collodion-tuberculin test, 521
- SMITH, C. RICHARD, AND OECHSLI, FRANK W. Sulfadiazine in experimental tuberculosis, 83
- SMITH, M. I., AND McCLOSKEY, W. T. Chemotherapy of sulfones and sulfonamides in experimental tuberculosis, 304
- SOTTILARO, JOSEPH J. See SINGER, PAUL, *et al.*, 521
- Specific cytotoxic action of tuberculin, 65
- STEWART, H. C. See PUFFER, RUTH R., *et al.*, 89
- Streptomycin in experimental tuberculosis, 269, 432
- Streptothricin in experimental tuberculosis, 299
- STRICKLAND, G. H., AND BOGEN, EMIL. Tuberculosis in a tropical naval hospital, 490
- Studies, Anatomical, on human tuberculosis, XVIII. Additional observations on progressive primary pulmonary tuberculosis in adults, 155
- XIX. Protracted primary tuberculosis in the adult, with some observations on "lymphoglandular-endogenous reinfection (Ghon)," 312
- XX. Disseminated calcified small nodular hematogenous pulmonary tubercles, incidentally discovered, 505
- Suction cabinet for use in cavity aspiration (Monaldi), 502
- Sulfadiazine in experimental tuberculosis, 83
- Sulfonamides, Chemotherapy of sulfones and, in experimental tuberculosis, 304
- Sulfones and sulfonamides, Chemotherapy of, in experimental tuberculosis, 304
- Survey, Tuberculosis, of food handlers on the Island of Oahu, 51
- TENNANT, ROBERT. See GERSTL, BRUNO, *et al.*, 58
- TERPLAN, KORNEL. Anatomical studies on human tuberculosis, XVIII. Additional observations on progressive pulmonary tuberculosis in adults, 155
- XIX. Protracted primary tuberculosis in the adult, with some observations on "lymphoglandular-endogenous reinfection (Ghon)," 312
- XX. Disseminated calcified small nodular hematogenous pulmonary tubercles, incidentally discovered, 505

- Test, collodion-tuberculin, Comparison of the tuberculin patch test and the, 521
 —, patch, tuberculin, and the collodion-tuberculin test, Comparison of the, 521
 —, —, —, Modified, 526
 THOMPSON, G. D. CARLYLE, AND BASS, H. E. Incidence of tuberculosis in Japanese-Americans, 46
 THOMPSON, JENCE F. See OLSON, KENNETH B., *et al.*, 474
 Thoracoplasty, 145, 258
 TITCHE, L. L. Tuberculosis of the tongue, 342
 Tongue, Tuberculosis of the, 342
 Transient focal pulmonary edema, 1
 Treatment of pulmonary tuberculosis with diasone, 474
 Tropical naval hospital, Tuberculosis in a, 490
 Tubercles, pulmonary, hematogenous, Disseminated calcified small nodular, incidentally discovered, 505
 Tuberculin patch test and the collodion-tuberculin test, Comparison of the, 521
 — — —, Modified, 526
 — sensitivity, Degree of, 424
 —, Specific cytotoxic action of, 65
 Tuberculosis among Montana Indians, 104
 —, Bed rest in, 15
 —, Epidemiology of, in a mental hospital, 248
 —, experimental, Chemotherapy in, 73
 —, —, — of sulfones and sulfonamides in, 304
 —, —, Streptomycin in, 269, 432
 —, —, Streptothricin in, 299
 —, —, Sulfadiazine in, 83
 —, Family histories in, 231
 —, human, Anatomical studies on,
 XVIII. Additional observations on progressive primary pulmonary tuberculosis in adults, 155
 XIX. Protracted primary tuberculosis in the adult, with some observations on "lymphoglandular-endogenous reinfection (Ghon)," 312
 XX. Disseminated calcified small nodular hematogenous pulmonary tubercles, incidentally discovered, 505
 Tuberculosis in a tropical naval hospital, 490
 — — children, 392
 — — household associates, 89
 —, Incidence of, in Japanese-Americans, 46
 — of the tongue, 342
 —, primary, Protracted, in the adult, with some observations on "lymphoglandular-endogenous reinfection (Ghon)," 312
 —, pulmonary, Bronchography in,
 V. Artificial pneumothorax, 21
 VI. Thoracoplasty,
 Part 1, 145
 Part 2, 258
 —, —, primary, progressive, in adults, Additional observations on, 155
 —, —, Strict bed rest in, 483
 —, —, Treatment of, with diasone, 474
 —, resistance to, Enzymes as factors in, 58
 — survey of food handlers on the Island of Oahu, 51
 VOLLMER, HERMANN. See SINGER, PAUL, *et al.*, 521
 WHELCHER, FRED C., AND CROW, HORACE E. Diaphragmatic paralysis and pneumoperitoneum, 367
 WILES, F. J. See DORMER, B. A., *et al.*, 21, 145, 258
 WILLIS, HENRY STUART, AND PECK, WILLIAM M. Bed rest in tuberculosis, 15
 WINN, WILLIAM DOUGLAS, AND ANDERSON, NORMAN LARUE. Pneumoperitoneum and diaphragmatic paralysis, 380
 WOODRUFF, WARRINER. A suction cabinet for use in cavity aspiration (Monaldi), 502
 YOUNG, GUY P., AND MCCARTER, JOHN C. Streptomycin in experimental tuberculosis, 432
 ZINTHEO, CLARENCE J., JR. See OLSON, KENNETH B., *et al.*, 474

INDEX OF ABSTRACTS

- Abcles, H., and Leiner, G. C. Hemidiaphragmatic paralysis, 91
- Abreu, B. E., and Woodbury, R. A. Circulatory effects of gasps, yawns and sighs, 64
- , —. —. See Volpitto, P. P., *et al.*, 95
- Abscess, Lung, 74
- , —, and tuberculosis, 29
- Absence of lung, Congenital, 8, 84
- — ribs, Congenital, 91
- Acid, α -furancarboxylic, amido-compounds of, Chemotherapy with, 48
- , Mycrocercic, 46
- Acid-fast microorganisms, Atypical, 45
- Acids, fatty, branched chain, Methyl groups in, 46
- , —, Dextrorotatory, in tubercle bacilli, 46
- Acne, Sensitivity to tuberculin in, 111
- Actinomycosis, 70
- and diabetes, 70
- Activation of specific proteolytic enzymes, 114
- Acute empyema, 10
- pneumonitis, 72
- Adamesik, F., and Erdély, J. Tuberculosis of stomach and cancer, 58
- Adenopathy, hilar, Diagnosis of, 56
- Adrenal amyloidosis, 93
- cortex and pulmonary tuberculosis, 26
- Adroque, E., and Tiscornia, B. G. Tuberculosis of eye, 60
- Agular, D. Closure of bronchocutaneous fistula with muscle flap, 56
- Air, alveolar, Oxygen tension of arterial blood and, 63
- Albumin, Serum, food for tubercle bacilli, 43
- Alexander, T. O. Irradiation pneumonitis, 77
- Alfoeldy, J. Antibodies in tuberculosis, 114
- Allergy, tuberculin, Seasonal, 50
- Allison, P. R. Acute empyema, 10
- Altitudes, high, Hemoglobin at, 65
- Alveolar air, Oxygen tension of arterial blood and, 63
- "cell tumor," Bronchial origin of, 7
- Amazon region, Tuberculosis in, 98
- Amebiasis and tuberculosis, 31
- Amido-compounds of α -furancarboxylic acid, Chemotherapy with, 48
- p-Aminobenzoic acid, Pigment formed from, by tubercle bacilli, 45
- Amyloidosis, Adrenal, 93
- Anatomical findings, Tomography and, 106
- Anatomy of pleura and endothoracic fascia, 62
- Anchezar, B. See Elizalde, P. I., *et al.*, 50, 51
- Anderson, R. J., and Ginger, L. G. Dextrorotatory fatty acids in tubercle bacilli, 46
- , —. —., — —, —. —. Mycrocercic acid, 46
- , —. —., — —, —. —. Phthiocerol, 46
- André. See Bergeron, *et al.*, 24, 101
- Anemia in pulmonary tuberculosis, 110
- Anesthesia in bronchoscopy, 18
- Aneurysm, Tuberculous, 60
- Annular shadows, 79
- Anomaly of pulmonary artery, 93
- Anthracosilicosis, 83
- Antibacterial effects on tubercle bacilli, 49
- Antibiotics, Effect of, on tubercle bacilli, 50
- Antibodies in tuberculosis, 114
- , tuberculin, Precipitin test for, 113
- Antonescu-Mazilu, F. See Papilian, V., *et al.*, 85
- Apical cavities, Collapse therapy for, 35
- tuberculosis, Diagnosis of, 26
- Applebaum, I. L., and Shrager, J. Pneumonitis with malaria, 73
- Arloing, F., Berthet, E., and Viallier, J. Chronic chlorine poisoning and tuberculosis, 112
- Armed forces, Tuberculosis in, 97
- Army, Tuberculosis in the, 98
- Arrhythmia, Cardiac, 91
- Arterial blood and alveolar air, Oxygen tension of, 63
- Artery, pulmonary, Anomaly of, 93
- , —, Dilatation of, 19
- Arthrodesis in tuberculosis of hip, 61
- Artifacts in staining of tubercle bacilli, 41
- Artificial respiration, 95
- Aspiration, Intracavitary, 38
- Aste-Salazar, H., and Hurtado, A. Hemoglobin at high altitudes, 65
- Asthma, Bronchial, 4
- , Spontaneous pneumothorax in, 5
- Atelectasis in pneumothorax, 32
- Atypical acid-fast microorganisms, 45
- pneumonia, 71
- —, Rib fractures in, 72
- Auerbach, O., and Stemmerman, Marguerite G. Adrenal amyloidosis, 93

- Austoniu and Marfori. Spontaneous pneumothorax, 6
- Aznarez, E. P. Lung abscess and tuberculosis, 29
- Bacilli, tubercle, Antibacterial effects on, 49
 —, —, Chemistry of, 114
 —, —, Cultivation of, 42
 —, —, Culture medium for, 42
 —, —, Demonstration of, 43
 —, —, Dextrorotatory fatty acids in, 46
 —, —, Effect of antibiotics on, 50
 —, —, food for, Serum albumin, 43
 —, —, Growth of, in blood, 43
 —, —, heat-killed, Vaccination with, 24, 25
 —, —, in feces, 42
 —, —, Method of testing bacteriostatic agents on, 48
 —, —, Pigment formed from p-aminobenzoic acid by, 45
 —, —, staining of, Artifacts in, 41
 —, —, Subsurface growth of, 44
 —, —, Sulfanilamide and, 47
- Bacillus, Tubercle, and endocrine diseases, 62
- Bacteriostatic agents, Method of testing, on tubercle bacilli, 48
 — property of culture filtrates, 49
- Baffoni, A. Glucose tolerance in pulmonary tuberculosis, 105
 —, —, Rupoli, L., and Spadoni, M. Glycolysis *in vitro* in tuberculosis, 110
- Bagassosis, 4
- Ballesterio, R. Spontaneous hemopneumothorax, 82
- Banyai, A. L., and Cadden, A. V. Diabetes and tuberculosis, 30
- Bariéty, P. M., Lerchboullet, J., and Gravois, R. Tuberculosis and respiratory system, 25
- Barret, N. R. Lung abscess, 74
- Bass, A. D., and Owens, J. N., Jr. Tuberculous aneurysm, 60
- Batista, D. Tuberculosis in Amazon region, 98
- Battle injuries of chest, 24
- Baumann, H. Eosinophilic pleuritis, 9
- Baylin, G. J. Cystic fibrosis of pancreas, 90
- Beckmann, A. Diagnosis of apical tuberculosis, 26
- Belli, N., and Maccone, V. Posthemoptotic pulmonary lesions, 26
- Belou, A. P., and Capdevila, C. Subclavophrenic nerve, 32
- Bence, A. E., and Vaccarezza, R. F. Treatment of tuberculous bronchitis, 53
- Benson, M., and King, A. C. Bilateral spontaneous pneumothorax, 5
- Bergeron, André, Bucquoy and Beust. Negative tuberculin tests in children, 101
 —, —, —, —, —. Tuberculin tests in children, 24
- Berthet, E. See Arloing, F., *et al.*, 112
- Bertola, V. J., and Ferraris, A. Primary tuberculosis of palate, 57
- Betancourt, J. R. Tuberculosis in infant, 100
- Beust. See Bergeron, *et al.*, 24, 101
- Bigger, I. A. See Ozlin, W. J., *et al.*, 87
- Bilateral pleurisy and phlebitis, 56
 — spontaneous pneumothorax, 5
- Bilirubinemia in tuberculosis, 110
- Blades, B., and Dugan, D. J. Resection of vagus nerve, 9
- Blastomycosis of lung, 70
- Blom, K. F. Vitamin K in hemoptysis, 26
- Blood, arterial, and alveolar air, Oxygen tension of, 63
 —, Growth of tubercle bacilli in, 43
- Blood-pressure and respiration, 63
- Bobb, A. L., and Fox, T. T. Cardiac arrhythmia, 91
- Boeck's sarcoid, Skin reaction in, 52
- Boffi, L. L. See Elizalde, P. I., *et al.*, 85
- Boller, R. Therapeutic cutaneous emphysema, 57
- Bondi, J. L., Scartascina, R., and Lamolla, F. A. Roentgenograms in dispensary, 23
- Bortagaray, M. C. Thoracoplasty, 37
- Boulanger, P. See Wasembourg, H., *et al.*, 105
- Bowie, E. R., and Jacobson, H. G. Routine chest roentgenography, 23
- Braginskaja, F. I., and Majanz, A. O. Intrapleural pneumonolysis in children, 33
- Branchetto-Brian, D., and Lascano, E. F. Anomaly of pulmonary artery, 93
- Brandes, W. W., Cook, R. A., and Osborne, M. P. Emphysema and lymphoid hyperplasia, 3
- Brazil, tuberculosis in, Fight against, 99
- Brette, P. See Dumarest, F., *et al.*, 38
- Brock, B. C. Bronchial carcinoma, 6
- Bronchi, Patent, 54
 —, Tuberculosis of trachea and, 54
- Bronchial asthma, 4
 — cancer, 87, 88
 — —, Diagnosis of, 88
 — carcinoma, 6, 87
 — origin of "alveolar cell tumor," 7
 — stenosis, 108
- Bronchiectasis, 76
- Bronchitis, tuberculous, Treatment of, 53

- Bronchocutaneous fistula, Closure of, with muscle flap, 56
- Bronchogenic cysts, 78
— tuberculosis, 104
- Broncholithiasis, 108
- Bronchopneumonia, Suppurative, 75
- Bronchopulmonary tumors, 86
- Bronchoscopy, Anesthesia in, 18
- Brunner, A. Surgical treatment of cavities, 37
- Bryce, A. G., and Mills, E. M. Pregnancy after lobectomy, 83
- Bucquoy. See Bergeron, *et al.*, 24, 101
- Bullae, Emphysematous, 82
- Bunker, P. G. Foreign bodies, 85
- Cadden, A. V., and Banyai, A. L. Diabetes and tuberculosis, 30
- Cahn, G. See Cisneros, A., *et al.*, 59
- Calcifications, Miliary, 26
- Cammann, O. Enterogenous tuberculosis, 58
- Cancer, Bronchial, 87, 88
—, —, Diagnosis of, 88
— of lung, 86
—, Tuberculosis of stomach and, 58
- Capdevila, C., and Belou, A. P. Subclavio-phrenic nerve, 32
- Capdeville, L. See Peña, J., *et al.*, 28
- Caputo, G. See Remolar, J. M., *et al.*, 66
- Carbohydrate, tuberculo-, and phosphatide, Inhibitory action of, 48
- Carcinoma, Bronchial, 6, 87
— of trachea, 89
- Cardiac arrhythmia, 91
- Carlisle, J. M. Pulmonary edema, 5
- Carotin in pulmonary tuberculous foci, 47
- Carpenter, E. E. Treatment of empyema, 12
- Carroll, D. S., and Ciaglia, P. Battle injuries of chest, 24
- Cathepsin, Inhibition of, by tuberculin, 52
- Cavernous tuberculosis in infant, 101
- Cavitary images, False, 106
- Cavitation, Nontuberculous, 79
- Cavities, apical, Collapse therapy for, 35
—, residual, Revision thoracoplasty for, 36
—, Surgical treatment of, 37
—, Tuberculous, 106
- Chagett, O. T., and Shepard, V. D. Chronic empyema, 11
- Chapman, A. S. See Pease, P. P., *et al.*, 82
- Chassagne, P., and Turpin, R. Cavernous tuberculosis in infant, 101
- Cheale, J. M., and Young, F. H. Prognosis after pneumonectomy, 29
- Chemistry of tubercle bacilli, 114
- Chemotherapy with amido-compounds of α -furancarboxylic acid, 48
- Cheney, G., and Denenholz, E. J. Coccidioidomycosis, 69
- Chertkova, E. I., and Chpanir, F. L. Chemotherapy with amido-compounds of α -furancarboxylic acid, 48
- Chest, Battle injuries of, 24
— examinations, Photoroentgen, 22
—, Fungus diseases of, 68
—, New growths of, 8
— roentgenography, Routine, 23
— surgery, Reconditioning after, 39
— surveys, Photofluorography for, 96
— wounds, 15
—, — of, 13
— —, open, Closure of, 16
— —, Penetrating, 16
— X-ray examination, 102
- Children, Intrapleural pneumonolysis in, 33
—, Negative tuberculin tests in, 101
—, school, Prophylaxis of tuberculosis in, 21
—, Tuberculin tests in, 24
- Chlorine poisoning, Chronic, and tuberculosis, 112
- Chpanir, F. L., and Chertkova, E. I. Chemotherapy with amido-compounds of α -furancarboxylic acid, 48
- Christie, R. V. Emphysema, 1
- Chronic chlorine poisoning and tuberculosis, 112
— colitis, Miliary tuberculosis and, 31
— empyema, 11
— —, Unusual cause of, 12
— miliary tuberculosis, 27
— myeloid leukemia, 19
- Chyllothorax, 10
- Ciaglia, P., and Carroll, D. S. Battle injuries of chest, 24
- Cimino, A. Bilirubinemia in tuberculosis, 110
- Circulation, Intrathoracic pressure and, 64
- Circulatory effects of gasps, yawns and sighs, 64
- Cisneros, A., Parisi, J., and Cahn, G. Tuberculosis and hydatid cyst of kidney, 59
- Closure of bronchocutaneous fistula with muscle flap, 56
— — open chest wounds, 16
- Clotted hemothorax, 12
- Coccidioidomycosis, 69
- Cohen, S. Costa reaction, 39
- Cohn, B. N. E. Congenital absence of ribs, 91
- Colburn, J. R. Coccidioidomycosis, 69
- Colitis, chronic, Miliary tuberculosis and, 31
- Collapse therapy for apical cavities, 35

- Complications after lobectomy, 83
- Comroe, J. H., Jr., and Dripps, R. D., Jr.
Oxygen tension of arterial blood and alveolar air, 63
- Congenital absence of lung, 8, 84
— — — ribs, 91
- Cook, R. A. See Brandes, W. W., *et al.*, 3
- Cornet, A. See Jacquelin, A., *et al.*, 104
- Cortex, Adrenal, and pulmonary tuberculosis, 26
- Costa reaction, 39
- Coste, F., LaMotte, M., and Guiot, G.
Histamine in treatment of sweating, 105
- Crivellari, C. A., and Steinber, I. R. Men-
ingitis and tuberculosis of uterus, 60
- Cruz Arnedo, F., and Fernandez Luna, D.
Duodenal tuberculous ulcer, 58
- Crysler, W. E. Atypical pneumonia, 71
- Cuculicchio, C. See Unchalo, D., *et al.*, 78
- Cultivation of tubercle bacilli, 42
- Culture filtrates, Bacteriostatic property of, 49
— medium for tubercle bacilli, 42
- Cutaneous emphysema, Therapeutic, 57
- Cyst, Hydatid, 78
—, —, and tuberculosis, 31
—, —, of kidney, Tuberculosis and, 59
- Cystic disease and dextroaortic arch, 79
- Cystic fibrosis of pancreas, 90
- Cysts, Bronchogenic, 78
- D'Abreu, A. L., Litchfield, J. W., and Hodson,
C. J. Intrathoracic foreign bodies, 13
- de Abreu, M. Pulmonary lavage, 40
— —. Tuberculosis survey among
healthy persons, 22
- de Almeida Prado, A. Blastomycosis of lung,
70
- de Goycochea, O. L. Complications after
lobectomy, 83
- Deitrick, J. E. See Ferguson, F. C., *et al.*, 93
- Delbecq, E., and Garnier, A. Fleeting pul-
monary infiltrates, 74
- del Carril, M. M. Right middle lobe pneu-
monia, 73
- del Castillo, E. B. Tubercle bacillus and
endocrine diseases, 62
- Demonstration of tubercle bacilli, 43
- Denenholz, E. J., and Cheney, G. Coccidi-
oidomycosis, 69
- Dermatology, Koch's discoveries and, 62
- Dermatoses, Patch and Mantoux tests in, 111
- Desbordes, J., and Paraf, J. Chemistry of
tubercle bacilli, 114
- Desensitization, Tuberculin, 51
—, —, Histamine and, 50
- Desmoules, R., Rousseau, L., Giroux, M., and
Richard, P. Diasone in pulmonary tu-
berculosis, 28
- Dextroaortic arch, Cystic disease and, 79
- Dextrorotatory fatty acids in tubercle bacilli,
46
- Dhar, D. R. Amebiasis and tuberculosis, 31
- Diabetes, Actinomycosis and, 70
— and tuberculosis, 29, 30
- Diagnosis of apical tuberculosis, 26
— — bronchial cancer, 88
— — hilar adenopathy, 56
- Diaphragm, Spontaneous paralysis of, 91
- Diaphragmatic paralysis, Spontaneous, 18
- Diasone, 107
— in guinea pig tuberculosis, 47
— — pulmonary tuberculosis, 28
- Diet in pulmonary tuberculosis, 27
- Dighiero, J. C., and Piaggio Blanco, R. A.
Tuberculous tracheobronchitis, 55
- Dilatation of pulmonary artery, 19
- Disease, Cystic, and dextroaortic arch, 79
—, Hodgkin's, 90
—, Pulmonary, and mega-esophagus, 85
- Diseases, endocrine, Tubercle bacillus and, 62
—, Fungus, of chest, 68
— of lung, Pilocarpin in, 85
- Dispensary, Roentgenograms in, 23
- Dorsey, J. M. Unusual cause of chronic
empyema, 12
- Drainage, Postural, in pulmonary tuberculosis,
106
- Drea, W. F. Antibacterial effects on tubercle
bacilli, 49
- Dripps, R. D., Jr., and Comroe, J. H., Jr.
Oxygen tension of arterial blood and
alveolar air, 63
- Dufourt, A., and Mounier-Kuhn, P. Hemor-
rhagic tracheobronchitis, 108
- Dugan, D. J., and Blades, B. Resection of
vagus nerve, 9
- Dumarest, F., Brette, P., and Germain, J.
Intracavitary aspiration, 38
- Duodenal tuberculous ulcer, 58
- Duran, H. See Juricic, B., *et al.*, 56
- Edema, Pulmonary, 5
- Edilio, B. Influence of hormones on tuber-
culin reaction, 52
- Edwards, P. W., and Penman, A. C. Primary
tuberculous infection, 101
- Electrobiogenesis, 63

- Elizalde, P. I., Latienda, R. I., and Boffi, L. L. Fibrolipoma of lung, 85
- , —, —, Monserrat, J. L., and Anchezar, B. Histamine and tuberculin desensitization, 50
- , —, —, Otoiz, O., and Anchezar, B. Tuberculin desensitization, 51
- Emmart, E. W., and Smith, M. I. Action of extracts of penicillium upon experimental tuberculosis, 107
- Emmler, A. Extrapleural pneumonolysis, 34
- Emphysema, 1, 3
- and lymphoid hyperplasia, 3
- , cutaneous, Therapeutic, 57
- , Interstitial, of lungs, 79
- of lung, 81
- — mediastinum, 82
- Emphysematous bullae, 82
- Empyema, Acute, 10
- , Chronic, 11
- , —, Unusual cause of, 12
- , Treatment of, 12
- Endocrine diseases, Tubercle bacillus and, 62
- Endothoracic fascia, Anatomy of pleura and, 62
- Enteritis, Regional, 20
- Enterogenous tuberculosis, 58
- Enzymes in tuberculous pus, 45
- , protcolytic, specific, Activation of, 114
- Eosinophilic lung infiltrations, 74
- pleuritis, 9
- Epituberculosis, 28
- Erdély, J., and Adamesik, F. Tuberculosis of stomach and cancer, 58
- Erythematodes, Lupus, familialis, 19
- Evans, W. A., and Galinsky, L. J. Bronchiectasis, 76
- Examination, X-ray, Chest, 102
- Examinations, chest, Photoroentgen, 22
- Experimental tuberculosis, Action of extracts of penicillium upon, 107
- Extrapleural pneumonolysis, 34
- pneumothorax, 33
- Extrapulmonary tuberculosis, 53
- —, Pulmonary and, 53
- Eye, Tuberculosis of, 60, 61
- False cavitory images, 106
- Familialis, Lupus erythematodes, 19
- Fascia, endothoracic, Anatomy of pleura and, 62
- Fatti, L., and Morton, H. J. V. Anesthesia in bronchoscopy, 18
- Fatty acids, branched chain, Methyl groups in, 46
- —, Dextrorotatory, in tubercle bacilli, 46
- — liver, 113
- — in tuberculosis, 30
- Feces, Tubercle bacilli in, 42
- Ferguson, C. F., and Neuhauser, E. B. D. Congenital absence of lung, 84
- Ferguson, F. C., Kobilak, R. E., and Deitrick, J. E. Hemoptysis in mitral stenosis, 93
- Fernandez Luna, D., and Cruz Arnedo, F. Duodenal tuberculous ulcer, 58
- —, —, —, Latienda, R. I. Tuberculosis of stomach, 57
- Ferraris, A., and Bertola, V. J. Primary tuberculosis of palate, 57
- Fibrolipoma of lung, 85
- Fibrosis, Cystic, of pancreas, 90
- Fierro Vignoli, M. Fleeting pulmonary infiltrate, 73
- Fight against tuberculosis in Brazil, 99
- Filtrates, culture, Bacteriostatic property of, 49
- Findings, anatomical, Tomography and, 106
- Fine, J. M., and Melamed, A. Ornithotic pneumonia, 72
- Fistula, bronchocutaneous, Closure of, with muscle flap, 56
- Fite, G. L., and Olson, B. J. Infectivity of mycobacteria, 44
- Flahiff, E. W., and Wells, C. W. Vaccination with heat-killed tubercle bacilli, 24
- , —, —. See Wells, C. W., *et al.*, 25
- Flap, muscle, Closure of bronchocutaneous fistula with, 56
- Fleeting pulmonary infiltrate, 73
- — infiltrates, 73, 74
- Florentin, P., Grandpierre, R., Grognot, P., and Royer, J. Fatty liver, 113
- Fluorescence microscopy, 44
- Foci, tuberculous, pulmonary, Carotin in, 47
- Fongi, E. G. Emphysema of mediastinum, 82
- Food for tubercle bacilli, Serum albumin, 43
- Foreign bodies, 85
- —, Intrathoracic, 13
- Foster, H. W., and Woodruff, H. B. Inhibition of mycobacterium by streptothricin, 50
- Fox, T. T., and Bobb, A. L. Cardiac arrhythmia, 91
- Fractures, Rib, in atypical pneumonia, 72
- Freedlander, B. L. Tuberculostatic action of phenothiazine, 49

- Friedman, B. See Romendick, S. S., *et al.*, 102
 Function, Respiratory, in pneumothorax, 32
 Fungus diseases of chest, 68
 α -Furancarboxylic acid, amido-compounds of,
 Chemotherapy with, 48
- Galinsky, L. J., and Evans, W. A. Bronchiectasis, 76
 Galy, P., and Policard, A. Anatomy of pleura and endothoracic fascia, 62
 Garcia Pérez, T. Extrapulmonary tuberculosis, 53
 Garnier, A., and Delbecq, E. Fleeting pulmonary infiltrates, 74
 Gasps, yawns and sighs, Circulatory effects of, 64
 Geever, E. F. Miliary calcifications, 26
 Generalized tuberculosis, 104
 Germain, J. See Dumarest, F., *et al.*, 38
 Gimeno, O. A. Culture medium for tubercle bacilli, 42
 Gines, A. R., and Wasmosi, A. Seasonal tuberculin allergy, 50
 Ginger, L. G. Methyl groups in branched chain fatty acids, 46
 —, —, —, and Anderson, R. J. Dextro-rotatory fatty acids in tubercle bacilli, 46
 —, —, —, —, —, —, —, —. Myco-cerosic acid, 46
 —, —, —, —, —, —, —, —. Phthiocerol, 46
 Giroux, M. Diasone in guinea pig tuberculosis, 47
 —, —. See Desmeules, R., *et al.*, 28
 Glover, R. E. Tuberculous infection of mice, 52
 Glucose tolerance in pulmonary tuberculosis, 105
 Glycolysis *in vitro* in tuberculosis, 110
 Goggio, A. F. Emphysema of lung, 81
 Gonzalez, F. M. See Raimondi, A. A., *et al.*, 106
 Gonzalez, G. See Juricic, B., *et al.*, 56
 Gordon, B. L. Tuberculosis of eye, 61
 Gordon, I. Emphysema, 3
 Gordon, J., and Walker, G. Plasmocytoma of lung, 88
 Graham, E. A., and Valle, A. R. Congenital absence of lung, 8
 Grandpierre, R. See Florentin, P., *et al.*, 113
 Granulations, Pathological, in leucocytes, 109
 Gravois, R. See Bariéty, P. M., *et al.*, 25
 Greco, N. V. Koch's discoveries and dermatology, 62
- Grobli, C. W. Spontaneous paralysis of diaphragm, 91
 Grognot, P. See Florentin, P., *et al.*, 113
 Grow, J. B., Raines, O. M., and Huddleston, O. L. Reconditioning after chest surgery, 39
 Growth of tubercle bacilli in blood, 43
 —, Subsurface, of tubercle bacilli, 44
 Growths, New, of chest, 8
 Guayaquil, Tuberculosis mortality in, 99
 Guinea pig tuberculosis, Diasone in, 47
 Guiot, G. See Coste, F., *et al.*, 105
 Gundersen, S. Atypical pneumonia, 71
 Guzman, A., and Llodra, G. Epituberculosis, 28
- Halliday, Nellie, and Weiss, C. Inhibition of cathepsin by tuberculin, 52
 —, —, —, —, —. Inhibitory action of tuberculo-carbohydrate and phosphatide, 48
 Hardisty, N. M., and Mitton, K. L. Cancer of lung, 86
 Harris, A. M., and Priestley, J. B. Actinomycosis, 70
 Harvey, R. M. Rib fractures in atypical pneumonia, 72
 Hauduroy, P. Demonstration of tubercle bacilli, 43
 —, —. Tuberculin, 99
 Hauser, H. See Wolpaw, S. E., *et al.*, 90
 Heaf, F. Work in tuberculosis, 102
 "Healthy" persons, Survey of, 22
 —, Tuberculosis survey among, 22
 Heat-killed tubercle bacilli, Vaccination with, 24, 25
 Heatley, T. F., Kahn, D., and Rex, C. R. Silicosis, 4
 Heimann, H. L., and Posel, M. M. Dilatation of pulmonary artery, 19
 Heinle, R. W., and Weir, D. R. Chronic myeloid leukemia, 19
 Hemidiaphragmatic paralysis, 91
 Hemoglobin at high altitudes, 65
 Hemopneumothorax, Spontaneous, 82
 Hemoptysis in mitral stenosis, 93
 —, Vitamin K in, 26
 Hemorrhagic tracheobronchitis, 108
 Hemothorax, Clotted, 12
 Herbut, P. A. Bronchial origin of "alveolar cell tumor," 7
 Herpel, F. K., and Zanca, P. Photoroentgen chest examinations, 22
 Heydemann, J., and Johnston, W. A. Pulmonary mycosis, 66

- Higgins, J. A. Tuberculosis mortality in Guayaquil, 99
- High altitudes, Hemoglobin at, 65
- Higley, C. S. See Wolpaw, S. E., *et al.*, 90
- Hilar adenopathy, Diagnosis of, 56
- Hip, tuberculosis of, Arthrodesis in, 61
- Hiroki, H. Growth of tubercle bacilli in blood, 43
- Histamine and tuberculin desensitization, 50
— in treatment of sweating, 105
- Hodgkin's disease, 90
- Hodson, C. J., and Litchfield, J. W. Penetrating chest wounds, 16
—, —. —. See D'Abreu, A. L., *et al.*, 13
- Holt, J. P. Intrathoracic pressure and circulation, 64
- Hormones, Influence of, on tuberculin reaction, 52
- Huddleston, O. L. See Grow, J. B., *et al.*, 39
- Hufford, C. E., and Sante, L. R. Annular shadows, 79
- Hultén, O. Revision thoracoplasty for residual cavities, 36
- Hurtado, A., and Aste-Salazar, H. Hemoglobin at high altitudes, 65
- Hydatid cyst, 78
— — and tuberculosis, 31
— — of kidney, Tuberculosis and, 59
- Hyperplasia, lymphoid, Emphysema and, 3
- Hypovitaminoses and tuberculosis, 105
- Ickert, F. Pulmonary and extrapulmonary tuberculosis, 53
- Infant, Cavernous tuberculosis in, 101
—, Tuberculosis in, 100
- Infection, Tuberculous, of mice, 52
—, —, Primary, 101
—, —, Transplacental, 111
- Infectivity of mycobacteria, 44
- Infiltrate, pulmonary, Fleeting, 73
- Infiltrates, pulmonary, Fleeting, 73, 74
- Infiltrations, lung, Eosinophilic, 74
- Ingrao, F., and Valli, A. Activation of specific proteolytic enzymes, 114
- Inhibition of cathepsin by tuberculin, 52
— — mycobacterium by streptothricin, 50
- Inhibitory action of tuberculo-carbohydrate and phosphatide, 48
- Injuries, Battle, of chest, 24
—, Thoracic, 15
- Interstitial emphysema of lungs, 79
- Intracavitary aspiration, 38
— contents, PH of, 110
- Intrapleural pneumonolysis in children, 33
- Intrathoracic foreign bodies, 13
— pressure and circulation, 64
- Irigoyen, L., and Izzo, R. A. Diagnosis of bronchial cancer, 88
- Irradiation pneumonitis, 77
- Izzo, R. A., and Irigoyen, L. Diagnosis of bronchial cancer, 88
- Jacobson, H. G., and Bowie, E. R. Routine chest roentgenography, 23
- Jacquelin, A., Cornet, A., and Villanova, P. Tuberculin therapy, 104
- Jaundice and tuberculosis, 30
- Jaworowska, A. D. Lupus erythematodes familiaris, 19
- Johnston, W. A., and Heydemann, J. Pulmonary mycosis, 66
- Jones, H. L., Jr., and Scott, W. G. Acute pneumonitis, 72
- Jones, Julia M., and Peck, W. M. Fatty liver in tuberculosis, 30
- Juricic, B., Gonzalez, G., and Duran, H. Diagnosis of hilar adenopathy, 56
- Kabuki, Y. Tuberculosis of stomach, 58
- Kahn, D. See Heatley, T. F., *et al.*, 4
- Kidney, hydatid cyst of, Tuberculosis and, 59
- King, A. C., and Benson, M. Bilateral spontaneous pneumothorax, 5
- Kobilak, R. E. See Ferguson, F. C., *et al.*, 93
- Koch's discoveries and dermatology, 62
- Kornblum, K. Bronchiectasis, 76
- Kuhn, A. J. See Stein, G. H., *et al.*, 6
- Kupka, E., and Oechsli, W. R. Intracavitary aspiration, 38
- Kvachnin, D. S. Extrapleural pneumothorax, 33
- Kveim, A. Skin reaction in Boeck's sarcoid, 52
- Lages Netto, D. J. Pneumopericardium, 18
- Lamolla, F. A. See Bondi, J. L., *et al.*, 23
- LaMotte, M. See Coste, F., *et al.*, 105
- Lascano, E. F., and Branchetto-Brian, D. Anomaly of pulmonary artery, 93
- Latienda, R. I., and Fernandez Luna, D. Tuberculosis of stomach, 57
—, —. —. See Elizalde, P. I., *et al.*, 85
- Lavage, Pulmonary, 40
- Leiner, G. C., and Abeles, H. Hemidiaphragmatic paralysis, 91
- Lempert, H. Fluorescence microscopy, 44
- Lereboullet, J. See Bariéty, P. M., *et al.*, 25

- Lesions, pulmonary, Posthemoptoie, 26
 —, tuberculous, Sterilization of, 112
 Leucocytes, Pathological granulations in, 109
 Leukemia, myeloid, Chronic, 19
 Lew, E. A., and Long, E. R. Tuberculosis in armed forces, 97
 Libanio, S. Fight against tuberculosis in Brazil, 99
 Litchfield, J. W., and Hodson, C. J. Penetrating chest wounds, 16
 —, —. —. See D'Abreu, A. L., *et al.*, 13
 Liver, Fatty, 113
 —, —, in tuberculosis, 30
 Llodra, G., and Guzman, A. Epituberculosis, 28
 Lobectomy, Complications after, 83
 —, Pregnancy after, 83
 Loeffler's syndrome, 74
 Loeschke, H., Loosc, K., and Schoedel, W. Blood-pressure and respiration, 63
 Long, E. R., and Lew, E. A. Tuberculosis in armed forces, 97
 Loose, K. See Loeschke, H., *et al.*, 63
 Lower lung field tuberculosis, 102
 Lung abscess, 74
 — and tuberculosis, 29
 —, Blastomycosis of, 70
 —, Cancer of, 86
 —, Congenital absence of, 8, 84
 —, diseases of, Pilocarpin in, 85
 —, Emphysema of, 81
 —, Fibrolipoma of, 85
 — infiltrations, Eosinophilic, 74
 —, Plasmocytoma of, 88
 —, Tumor of, 87
 Lungs, Interstitial emphysema of, 79
 Lupus erythematoses familiaris, 19
 Lush, R. W., and Nicholson, J. C. Clotted hemothorax, 12
 Lymphoid hyperplasia, Emphysema and, 3
 Lynch, T. W. Sensitivity to tuberculin in acne, 111
 Maccione, V., and Belli, N. Posthemoptoie pulmonary lesions, 26
 MacDonald, W. C., and Muether, R. O. Precipitin test for tuberculin antibodies, 113
 Macklin, C. C., and Macklin, Madge Thorlow. Interstitial emphysema of lungs, 79
 Macklin, Madge Thorlow, and Macklin, C. C. Interstitial emphysema of lungs, 79
 Mainetti, J. M. See Unchalo, D., *et al.*, 78
 Majanz, A. O., and Braginskaja, F. I. Intrapleural pneumonolysis in children, 33
 Malaria, Pneumonitis with, 73
 Mantoux and patch tests in dermatoses, 111
 Manzini, C. Carotin in pulmonary tuberculous foci, 47
 Marfori and Austonu. Spontaneous pneumothorax, 6
 Mason, M. W. Photofluorography for chest surveys, 96
 Mass surveys, 95
 Matte, R., and Saldias, E. Tuberculous pleurisy, 57
 Matteo, A. L. Pulmonary syphilis, 65
 Mattina, M. Fleeting pulmonary infiltrates, 73
 Mayer, E., and Rappaport, I. Prephthisical tuberculosis, 103
 Mayer, R. L. Pigment formed from p-aminobenzoic acid by tubercle bacilli, 45
 —, —. —. Sulfanilamide and tubercle bacilli, 47
 McCarter, J. R., and Powelson, D. M. Cultivation of tubercle bacilli, 42
 —, —. —, —, —, —. —. Serum albumin, food for tubercle bacilli, 43
 McCloskey, B. J. Anthracosilicosis, 83
 McConkie, E. B. See Stein, G. H., *et al.*, 6
 McGrath, E. J. Wounds of chest, 13
 Mediastinal tumors, 89
 Mediastinum, Emphysema of, 82
 Medium, Culture, for tubercle bacilli, 42
 Meerloo, A. M. Tumor of lung, 87
 Mega-esophagus, Pulmonary disease and, 85
 Melamed, A., and Fine, J. M. Ornithotic pneumonia, 72
 Meningitis and tuberculosis of uterus, 60
 Mesothelioma of pleura, 89
 Methyl groups in branched chain fatty acids, 46
 Mice, Tuberculous infection of, 52
 Microorganisms, acid-fast, Atypical, 45
 Microscopy, Fluorescence, 44
 Middle lobe pneumonia, Right, 73
 Mihail, N. See Papilian, V., *et al.*, 85
 Miliary calcifications, 26
 — tuberculosis and chronic colitis, 31
 — —, Chronic, 27
 Miller, H. Eosinophilic lung infiltrations, 74
 Mills, E. M., and Bryce, A. G. Pregnancy after lobectomy, 83
 Mitral stenosis, Hemoptysis in, 93
 Mitton, K. L., and Hardisty, N. M. Cancer of lung, 86
 Moetsch, J. C. See Raiziss, G. W., *et al.*, 107
 Monaldi, V. Intracavitary aspiration, 38
 Monserrat, J. L. See Elizalde, P. I., *et al.*, 50

- Moreau, M., and Queirel, J. Cystic disease and dextroaortic arch, 79
- Morgenstern, P., and Nathanson, L. Non-tuberculous cavitation, 79
- Morse, D. G. Mass surveys, 95
- Mortality, Tuberculosis, in Guayaquil, 99
- Morton, H. J. V., and Fatti, L. Anesthesia in bronchoscopy, 18
- Mounier-Kuhn, P., and Dufourt, A. Hemorrhagic tracheobronchitis, 108
- Muether, R. O., and MacDonald, W. C. Precipitin test for tuberculin antibodies, 113
- Muscle flap, Closure of bronchocutaneous fistula with, 56
- Mycobacteria, Infectivity of, 44
- Mycobacterium, Inhibition of, by streptomycin, 50
- Mycocerosic acid, 46
- Mycosis, Pulmonary, 66
- Myeloid leukemia, Chronic, 19
- Myelchreest, W. H., and Scott, I. M. Generalized tuberculosis, 104
- Nathanson, L., and Morgenstern, P. Non-tuberculous cavitation, 79
- Negative tuberculin tests in children, 101
- Nerve, vagus, Resection of, 9
- Neuhauser, E. B. D., and Ferguson, C. F. Congenital absence of lung, 84
- Neuhof, H., and Thomas, A. Suppurative bronchopneumonia, 75
- New growths of chest, 8
- Nicholson, J. C., and Lush, R. W. Clotted hemothorax, 12
- Nielas, J. Pathological granulations in leucocytes, 109
- Nolli, B., and Pallazoli, M. Adrenal cortex and pulmonary tuberculosis, 26
- Nontuberculous cavitation, 79
- Northoff, H. Cultivation of tubercle bacilli, 42
- Nuti, M. Anemia in pulmonary tuberculosis, 110
- Obstmayer, J. Patent bronchi, 54
- Oechsli, W. R. Emphysematous bullae, 82
- , —, —, and Kupka, E. Intracavitary aspiration, 38
- Oefelein. Diet in pulmonary tuberculosis, 27
- Olsen, A. M., and Wilson, G. T. Chylothorax, 10
- Olson, B. J., and Fite, G. L. Infectivity of mycobacteria, 44
- Oosthuizen, S. F. Chest X-ray examination, 102
- Opacio, D., and Urzay, B. Survey of "healthy" persons, 22
- Open chest wounds, Closure of, 16
- Oppenheimer, A. "Virus" pneumonia, 71
- Oricchio, D., and Savarino, S. Bacteriostatic property of culture filtrates, 49
- Ornithotic pneumonia, 72
- Osacar, H. E. Bilateral pleurisy and phlebitis, 56
- , —, —. Chronic miliary tuberculosis, 27
- Osborne, M. P. See Brandes, W. W., *et al.*, 3
- Otoiz, O. See Elizalde, P., *et al.*, 51
- Owens, F. Regional enteritis, 20
- Owens, J. N., Jr., and Bass, A. D. Tuberculous aneurysm, 60
- Oxygen tension of arterial blood and alveolar air, 63
- Ozlin, W. J., Bigger, I. A., and Vinson, P. P. Bronchial cancer, 87
- Pagel, W. Bronchogenic tuberculosis, 104
- Palate, Primary tuberculosis of, 57
- Pallazoli, M., and Nolli, B. Adrenal cortex and pulmonary tuberculosis, 26
- Panà, C., and Torelli, G. Tomography and anatomical findings, 106
- Pancreas, Cystic fibrosis of, 90
- Papilian, V., Ursu, I., Mihail, N., and Antonescu-Mazilu, F. Pilocarpin in diseases of lung, 85
- Paraf, J., and Desbordes, J. Chemistry of tubercle bacilli, 114
- Paralysis, diaphragmatic, Spontaneous, 18
- , Hemidiaphragmatic, 91
- , Spontaneous, of diaphragm, 91
- Paredes, L., and Vaccaro, H. V. Transplantational tuberculous infection, 111
- Parisi, J. See Cisneros, A., *et al.*, 59
- Parodi, F. Electrobiogenesis, 63
- Pascher, F., and Sulzberger, M. B. Patch and Mantoux tests in dermatoses, 111
- Patch and Mantoux tests in dermatoses, 111
- Patent bronchi, 54
- Pathological granulations in leucocytes, 109
- Patients, tuberculous, Pericardium in, 60
- Pease, P. P., Steuer, L. G., and Chapman, A. S. Spontaneous pneumothorax, 82
- Peck, W. M., and Jones, Julia M. Fatty liver in tuberculosis, 30
- Pectus excavatum, 17

- Peña, E. See Peña, J., *et al.*, 28
- Peña, J., Peña, E., and Capdeville, L. Epi-
tuberculosis, 28
- Penetrating chest wounds, 16
- Penicillium, extracts of, Action of, upon ex-
perimental tuberculosis, 107
- Penman, A. C., and Edwards, P. W. Primary
tuberculous infection, 101
- Percz, J. A. Tuberculosis of trachea and
bronchi, 54
- Pericardium in tuberculous patients, 60
- Peritonitis, Tuberculous, 59
- Peterson, V. L. Fungus diseases of chest, 68
- Petrik, F. G. Atypical acid-fast microorgan-
isms, 45
- Petrillo, L. M. Prophylaxis of tuberculosis in
school children, 21
- PH of intracavitary contents, 110
- — pleural fluids, 110
- Phenothiazine, Tuberculostatic action of, 49
- Phlebitis, Bilateral pleurisy and, 56
- Phosphatide, tuberculo-carbohydrate and, In-
hibitory action of, 48
- Photofluorography for chest surveys, 96
- Photoroentgen chest examinations, 22
- Phrenic, Subclavian, nerve, 32
- Phthiocerol, 46
- Piaggio Blanco, R. A., and Dighiero, J. C.
Tuberculous tracheobronchitis, 55
- Pierson, P. H. Carcinoma of trachea, 89
- Pigment formed from p-aminobenzoic acid by
tubercle bacilli, 45
- Pilocarpin in diseases of lung, 85
- Plasmocytoma of lung, 88
- Pleura and endothoracic fascia, Anatomy of,
62
- , Mesothelioma of, 89
- Pleural fluids, PH of, 110
- Pleurisy, Bilateral, and phlebitis, 56
- , Tuberculous, 57
- Pleuritis, Eosinophilic, 9
- Pneumonectomy, Prognosis after, 29
- Pneumonia, Atypical, 71
- , —, Rib fractures in, 72
- , Ornithotic, 72
- , Right middle lobe, 73
- , "Virus," 71
- Pneumonitis, Acute, 72
- , Irradiation, 77
- with malaria, 73
- Pneumonolysis, Extrapleural, 34
- , Intrapleural, in children, 33
- Pneumopericardium, 18
- Pneumothorax, Atelectasis in, 32
- , Extrapleural, 33
- , Respiratory function in, 32
- , Spontaneous, 6, 82
- , —, Bilateral, 5
- , —, in asthma, 5
- Poisoning, chlorine, Chronic, and tuberculosis,
112
- Poiteau, J. See Wasembourg, H., *et al.*, 105
- Polieard, A., and Galy, P. Anatomy of pleura
and endothoracic fascia, 62
- Pongor, F. Jaundice and tuberculosis, 30
- Porter, K. R., and Yegian, D. Artifacts in
staining of tubercle bacilli, 41
- Posel, M. M., and Heimann, H. L. Dilatation
of pulmonary artery, 19
- Posthemoptotic pulmonary lesions, 26
- Postoloff, A. V. Mesothelioma of pleura, 89
- Postural drainage in pulmonary tuberculosis,
106
- Powelson, D. M., and McCarter, J. R. Cul-
tivation of tubercle bacilli, 42
- , —, —, —, —. Serum
albumin, food for tubercle bacilli, 43
- Precipitin test for tuberculin antibodies, 113
- Pregnancy after lobectomy, 83
- Prephthical tuberculosis, 103
- Pressure, Intrathoracic, and circulation, 64
- Priestley, J. B., and Harris, A. M. Actino-
mycosis, 70
- Primary tuberculosis of palate, 57
- tuberculous infection, 101
- Prognosis after pneumonectomy, 29
- Prophylaxis of tuberculosis in school children,
21
- Proteolytic enzymes, specific, Activation of,
114
- Pruvost, R., and Turet. False cavity images,
106
- Pullen, R. L., and Sodeman, W. A. Bagas-
sosis, 4
- Pulmonary and extrapulmonary tuberculosis,
53
- artery, Anomaly of, 93
- —, Dilatation of, 19
- disease and mega-esophagus, 85
- edema, 5
- infiltrate, Fleeting, 73
- infiltrates, Fleeting, 73, 74
- lavage, 40
- lesions, Posthemoptotic, 26
- mycosis, 66
- syphilis, 65, 66
- tuberculosis, Adrenal cortex and, 26

- Pulmonary tuberculosis, Anemia in, 110
 — — —, Diasone in, 28
 — — —, Diet in, 27
 — — —, Glucose tolerance in, 105
 — — —, Postural drainage in, 106
 — tuberculous foci, Carotin in, 47
 Pus, tuberculous, Enzymes in, 45
 Pyelogram in renal tuberculosis, 59
- Queirel, J., and Moreau, M. Cystic disease and dextroaortic arch, 79
- Raimondi, A. A., Scartaschini, R., and Gonzalez, F. M. Tuberculous cavities, 106
 Raines, O. M. See Grow, J. B., *et al.*, 39
 Raiziss, G. W., Severac, M., and Moetsch, J. C. Diasone, 107
 Randolph, T. G., and Rawling, F. A. Bronchial asthma, 4
 Rappaport, I., and Mayer, E. Prephthistical tuberculosis, 103
 Rawling, F. A., and Randolph, T. G. Bronchial asthma, 4
 Reaction, Costa, 39
 —, Skin, in Boeck's sarcoid, 52
 —, tuberculin, Influence of hormones on, 52
 Reconditioning after chest surgery, 39
 Regional enteritis, 20
 Remolar, J. M., Thompson, V., and Caputo, G. Pulmonary syphilis, 66
 Renal tuberculosis, Pyelogram in, 59
 Resection of vagus nerve, 9
 Residual cavities, Revision thoracoplasty for, 36
 Respiration, Artificial, 95
 —, Blood-pressure and, 63
 Respiratory function in pneumothorax, 32
 — system, Tuberculosis and, 25
 Revision thoracoplasty for residual cavities, 36
- Rex, C. R. See Heatley, T. F., *et al.*, 4
 Rib fractures in atypical pneumonia, 72
 Ribs, Congenital absence of, 91
 Richard, P. See Desmeules, R., *et al.*, 28
 Rimini, R. Actinomycosis and diabetes, 70
 Rivas, C. I. Hydatid cyst and tuberculosis, 31
 Robbins, L. L. Bronchogenic cysts, 78
 —, —. —. Mediastinal tumors, 89
 Rocca, J. B. Respiratory function in pneumothorax, 32
 Rocchio, I. Pericardium in tuberculous patients, 60
 Roentgenograms in dispensary, 23
 Roentgenography, chest, Routine, 23
 Romendick, S. S., Friedman, B., and Schwartz, H. F. Lower lung field tuberculosis, 102
 Roth, F. B. Arthrodesis in tuberculosis of hip, 61
 Rousseau, L. See Desmeules, R., *et al.*, 28
 Routine chest roentgenography, 23
 Royer, J. See Florentin, P., *et al.*, 113
 Rupoli, L. See Baffoni, A., *et al.*, 110
- Saenz, A. Sterilization of tuberculous lesions, 112
 St. Loup, E. Tuberculous peritonitis, 59
 Saldias, E., and Matte, R. Tuberculous pleurisy, 57
 Sante, L. R., and Hufford, C. E. Annular shadows, 79
 Sarcoid, Boeck's, Skin reaction in, 52
 Savarino, S., and Oricchio, D. Bacteriostatic property of culture filtrates, 49
 Scartaschini, R. See Raimondi, A. A., *et al.*, 106
 Scartascina, R. See Bondi, J. L., *et al.*, 23
 Schatz, A., and Waksman, S. A. Effect of antibiotics on tubercle bacilli, 50
 Schoedel, W. See Loeschcke, H., *et al.*, 63
 Scholz, B. Treatment of tuberculosis, 27
 School children, Prophylaxis of tuberculosis in, 21
 Schroeder, C. H. Pyelogram in renal tuberculosis, 59
 —, —. —. Tuberculosis in twins, 107
 Schwartz, H. F. See Romendick, S. S., *et al.*, 102
 Scott, I. M., and Mylechreest, W. H. Generalized tuberculosis, 104
 Scott, R. B. Chest wounds, 15
 Scott, W. G., and Jones, H. L., Jr. Acute pneumonitis, 72
 Seasonal tuberculin allergy, 50
 Sensitivity to tuberculin in acne, 111
 Serum albumin, food for tubercle bacilli, 43
 Severac, M. See Raiziss, G. W., *et al.*, 107
 Shadows, Annular, 79
 Shepard, V. D., and Chagett, O. T. Chronic empyema, 11
 Shrager, J., and Applebaum, I. L. Pneumonitis with malaria, 73
 Sighs, Circulatory effects of gasps, yawns and, 64
 Silicosis, 4
 Sinha, M. P. Diabetes and tuberculosis, 29
 Skin reaction in Boeck's sarcoid, 52
 Smith, H. H. See Wells, C. W., *et al.*, 25

- Smith, M. I., and Emmart, E. W. Action of extracts of penicillium upon experimental tuberculosis, 107
- Sodeman, W. A., and Pullen, R. L. Bagassosis, 4
- Spadoni, M. See Baffioni, A., *et al.*, 110
- Spandonari, A. Enzymes in tuberculous pus, 45
- Spontaneous diaphragmatic paralysis, 18
- hemopneumothorax, 82
- paralysis of diaphragm, 91
- pneumothorax, 6, 82
- —, Bilateral, 5
- — in asthma, 5
- Staining of tubercle bacilli, Artifacts in, 41
- Stein, G. H., McConkie, E. B., and Kuhn, A. J. Spontaneous pneumothorax, 6
- Steinber, I. R., and Crivellari, C. A. Meningitis and tuberculosis of uterus, 60
- Steiner, P. E. Bronchial carcinoma, 87
- Stemmerman, Marguerite G., and Auerbach, O. Adrenal amyloidosis, 93
- Stenosis, Bronchial, 108
- , mitral, Hemoptysis in, 93
- Sterilization of tuberculous lesions, 112
- Steuer, L. G. See Pease, P. P., *et al.*, 82
- Stomach, Tuberculosis of, 57, 58
- , — —, and cancer, 58
- Streptothricin, Inhibition of mycobacterium by, 50
- Subclavio-phrenic nerve, 32
- Subieta, R. A. Atelectasis in pneumothorax, 32
- Subsurface growth of tubercle bacilli, 44
- Sulfanilamide and tubercle bacilli, 47
- Sulzberger, M. B., and Pascher, F. Patch and Mantoux-tests in dermatoses, 111
- Suppurative bronchopneumonia, 75
- Surgery, chest, Reconditioning after, 39
- Surgical treatment of cavities, 37
- Survey of "healthy" persons, 22
- , Tuberculosis, among healthy persons, 22
- Surveys, chest, Photofluorography for, 96
- , Mass, 95
- Sweating, treatment of, Histamine in, 105
- Sweet, R. H. Pectus excavatum, 17
- Swyngedanw, J. See Wasembourg, H., *et al.*, 105
- Syndrome, Loeffler's, 74
- Syphilis, Pulmonary, 65, 66
- Tempel, C. W. New growths of chest, 8
- Tension, Oxygen, of arterial blood and alveolar air, 63
- Test, Precipitin, for tuberculin antibodies, 113
- Testing bacteriostatic agents on tubercle bacilli, Method of, 48
- Tests, Patch and Mantoux, in dermatoses, 111
- , Tuberculin, in children, 24
- , —, Negative, in children, 101
- Therapeutic cutaneous emphysema, 57
- Therapy, Collapse, for apical cavities, 35
- , Tuberculin, 104
- Thomas, A., and Neuhoof, H. Suppurative bronchopneumonia, 75
- Thomas, C. P. Thoracic injuries, 15
- Thompson, V. See Remolar, J. M., *et al.*, 66
- Thoracic injuries, 15
- Thoracoplasty, 35, 37
- , Revision, for residual cavities, 36
- Tiret, and Pruvost, R. False cavity images, 106
- Tiscornia, B. G., and Adrogue, E. Tuberculosis of eye, 60
- Tomography and anatomical findings, 106
- Torelli, G., and Panà, C. Tomography and anatomical findings, 106
- Trachea and bronchi, Tuberculosis of, 54
- , Carcinoma of, 89
- Tracheobronchitis, Hemorrhagic, 108
- , Tuberculous, 55
- Transplacental tuberculous infection, 111
- Traversa, A. Spontaneous diaphragmatic paralysis, 18
- Treatment of empyema, 12
- — sweating, Histamine in, 105
- — tuberculosis, 27
- — tuberculous bronchitis, 53
- , Surgical, of cavities, 37
- Trowbridge, M., Jr. Spontaneous pneumothorax in asthma, 5
- Tubercle bacilli, Antibacterial effects on, 49
- —, Chemistry of, 114
- —, Cultivation of, 42
- —, Culture medium for, 42
- —, Demonstration of, 43
- —, Dextrorotatory fatty acids in, 46
- —, Effect of antibiotics on, 50
- —, food for, Serum albumin, 43
- —, Growth of, in blood, 43
- —, Heat-killed, Vaccination with, 24, 25
- — in feces, 42
- —, Method of testing bacteriostatic agents on, 48
- —, Pigment formed from p-aminobenzoic acid by, 45

- Tubercle bacilli, staining of, Artifacts in, 41
 — —, Subsurface growth of, 44
 — —, Sulfanilamide and, 47
 — bacillus and endocrine diseases, 62
 Tuberculin, 99
 — allergy, Seasonal, 50
 — antibodies, Precipitin test for, 113
 — desensitization, 51
 — —, Histamine and, 50
 —, Inhibition of cathepsin by, 52
 — reaction, Influence of hormones on, 52
 —, Sensitivity to, in acne, 111
 — tests in children, 24
 — —, Negative, in children, 101
 — therapy, 104
 Tuberculosis, Amebiasis and, 31
 — and hydatid cyst of kidney, 59
 — — respiratory system, 25
 —, Antibodies in, 114
 —, apical, Diagnosis of, 26
 —, Bilirubinemia in, 110
 —, Bronchogenic, 104
 —, Cavernous, in infant, 101
 —, Chronic chlorine poisoning and, 112
 —, Diabetes and, 29, 30
 —, Enterogenous, 58
 —, experimental, Action of extracts of penicillium upon, 107
 —, Extrapulmonary, 53
 —, Fatty liver in, 30
 —, Generalized, 104
 —, Glycolysis *in vitro* in, 110
 —, guinea pig, Diasone in, 47
 —, Hydatid cyst and, 31
 —, Hypovitaminoses and, 105
 — in Amazon region, 98
 — — armed forces, 97
 — — Brazil, Fight against, 99
 — — infant, 100
 — — the army, 98
 — — twins, 107
 —, Jaundice and, 30
 —, Lower lung field, 102
 —, Lung abscess and, 29
 —, Miliary, and chronic colitis, 31
 —, —, Chronic, 27
 — mortality in Guayaquil, 99
 — of eye, 60, 61
 — — hip, Arthrodesis in, 61
 — — stomach, 57, 58
 — — and cancer, 58
 — — trachea and bronchi, 54
 — — uterus, Meningitis and, 60
 —, Prephthisical, 103
 Tuberculosis, Primary, of palate, 57
 —, Prophylaxis of, in school children, 21
 —, pulmonary, Adrenal cortex and, 26
 —, — and extrapulmonary, 53
 —, —, Anemia in, 110
 —, —, Diasone in, 28
 —, —, Diet in, 27
 —, —, Glucose tolerance in, 105
 —, —, Postural drainage in, 106
 —, renal, Pyelogram in, 59
 — survey among healthy persons, 22
 —, Treatment of, 27
 —, Work in, 102
 Tuberculostatic action of phenothiazine, 49
 Tuberculous aneurysm, 60
 — bronchitis, Treatment of, 53
 — cavities, 106
 — foci, pulmonary, Carotin in, 47
 — infection of mice, 52
 — —, Primary, 101
 — —, Transplacental, 111
 — lesions, Sterilization of, 112
 — patients, Pericardium in, 60
 — peritonitis, 59
 — pleurisy, 57
 — pus, Enzymes in, 45
 — tracheobronchitis, 55
 — ulcer, Duodenal, 58
 Tullini, F. Postural drainage in pulmonary tuberculosis, 106
 "Tumor, alveolar cell," Bronchial origin of, 7
 — of lung, 87
 Tumors, Bronchopulmonary, 86
 —, Mediastinal, 89
 Turpin, R., and Chassagne, P. Cavernous tuberculosis in infant, 101
 Twins, Tuberculosis in, 107
 Ulcer, tuberculous, Duodenal, 58
 Unchalo, D., Mainetti, J. M., and Cuculicchio, C. Hydatid cyst, 78
 Ursu, I. See Papilian, V., *et al.*, 85
 Urzay, B., and Opacio, D. Survey of "healthy" persons, 22
 Uterus, tuberculosis of, Meningitis and, 60
 Vaccarezza, R. F., and Bence, A. E. Treatment of tuberculous bronchitis, 53
 Vaccaro, H. V., and Paredes, L. Transplacental tuberculous infection, 111
 Vaccination with heat-killed tubercle bacilli, 24, 25

- Vagus nerve, Resection of, 9
- Valle, A. R., and Graham, E. A. Congenital absence of lung, 8
- Valli, A., and Ingrao, F. Activation of specific proteolytic enzymes, 114
- Viallier, J. See Arloing, F., *et al.*, 112
- Villanova, P. See Jacquelin, A., *et al.*, 104
- Villegas, J. C. Bronchial stenosis, 108
- Vinson, P. P. See Ozlin, W. J., *et al.*, 87
- "Virus" pneumonia, 71
- Vitamin K in hemoptysis, 26
- Volpitto, P. P., Woodbury, R. A., and Abreu, B. E. Artificial respiration, 95
- v. Meyenburg, H. Loeffler's syndrome, 74
- Voute, M. Tuberculosis in the army, 98
- Waksman, S. A., and Schatz, A. Effect of antibiotics on tubercle bacilli, 50
- Walker, G., and Gordon, J. Plasmocytoma of lung, 88
- Warcalde, J. G. Bronchopulmonary tumors, 86
- Wasembourg, H., Boulanger, P., Swyngedanw, J., and Poiteau, J. Hypovitaminoses and tuberculosis, 105
- Wasmosi, A., and Gines, A. R. Seasonal tuberculin allergy, 50
- Weens, H. S. Pulmonary disease and megasophagus, 85
- Weinstein, M. Closure of open chest wounds, 16
- Weir, D. R., and Heinle, R. W. Chronic myeloid leukemia, 19
- Weiss, C., and Halliday, Nellie. Inhibition of cathepsin by tuberculin, 52
- , —, —, —. Inhibitory action of tuberculo-carbohydrate and phosphate, 48
- Wells, C. W., and Flahiff, E. W. Vaccination with heat-killed tubercle bacilli, 24
- , —, —, Flahiff, E. W., and Smith, H. H. Vaccination with heat-killed tubercle bacilli, 25
- Widmann, B. P. Bronchial cancer, 88
- Wilson, G. T., and Olsen, A. M. Chylothorax, 10
- Wolf, J. E. Tubercle bacilli in feces, 42
- Wolpaw, S. E., Higley, C. S., and Hauser, H. Hodgkin's disease, 90
- Woodbury, R. A., and Abreu, B. E. Circulatory effects of gasps, yawns and sighs, 64
- , —, —. See Volpitto, P. P., *et al.*, 95
- Woodruff, H. B., and Foster, H. W. Inhibition of mycobacterium by streptothricin, 50
- Work in tuberculosis, 102
- Wounds, Chest, 15
- , —, open, Closure of, 16
- , —, Penetrating, 16
- of chest, 13
- X-ray examination, Chest, 102
- Yawns and sighs, Circulatory effects of gasps, 64
- Yegian, D., and Porter, K. R. Artifacts in staining of tubercle bacilli, 41
- Youmans, G. P. Method of testing bacteriostatic agents on tubercle bacilli, 48
- , —, —. Subsurface growth of tubercle bacilli, 44
- Young, F. H., and Cheale, J. M. Prognosis after pneumonectomy, 29
- Zanca, P., and Herpel, F. K. Photoroentgen chest examinations, 22
- Zirilli, G. PH of intracavitary contents, 110
- , —. PH of pleural fluids, 110
- Zweifel, E. Broncholithiasis, 108

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